

**The associations between physical activity, the severity
of obstructive sleep apnoea and its consequences**

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A thesis submitted in partial fulfilment of the requirements of Teesside
University for the degree of Doctor of Philosophy

April 2019

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Declaration

I declare that the work contained within this thesis is entirely my own work. I declare that any help received in preparing this thesis has been acknowledged accordingly. I declare that all sources used in the preparation of this thesis have been referenced appropriately. I declare that no material contained within this thesis has been used in any other submission for an academic award.

Acknowledgements

I would firstly like to acknowledge Teesside University who funded this thesis, granted me access to numerous resources to facilitate my learning and supported me through every step of the doctoral process. I feel extremely grateful to have had this opportunity.

I would like to express extreme gratitude to my supervisory team, in particular, Professor Greg Atkinson. You have been by my side throughout. Your exceptional guidance, especially with the statistical aspects of the work, matched with such genuine caring and compassion, has made this thesis possible. You are a truly outstanding Director of Studies. Professor Alan Batterham, thank you for your invaluable statistical direction and for believing in me from day one. I am blessed to have had your tutorage and support.

Professor Gerard Danjoux, thank you for facilitating and guiding me in the clinical aspects of this thesis. I am so grateful for your time, expertise and advice. I would also like to sincerely thank the patients who took part in the public involvement work and the team at James Cook University Hospital, including Dr Angela Habgood, who supported the clinical work.

Finally, thank you to my team, my family of support, for imparting the tools, the love and the belief that has fuelled me through the parts I thought were insurmountable, you made the difference. Thank you to my family, especially Chris, I could not have done this without you, and Christine, your love has been a light. Finally, I would like to express my sincere gratitude to my mum and dad. You both made this, and everything I do, possible. I know you are always by my side. This is for you.

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List of Abbreviations

AASM: American Academy of Sleep Medicine
ACSM: American College of Sports Medicine
AHI: apnoea-hypopnoea index
AUC: area under the receiver operating characteristic curve
BMI: body mass index
BQ: Berlin Questionnaire
CAD: coronary artery disease
CI: confidence interval
CPAP: continuous positive airway pressure
CPET: cardiopulmonary exercise testing
ECG: electrocardiogram
EEG: electroencephalogram
ESS: Epworth Sleepiness Scale
FMD%: percentage flow-mediated dilation of the brachial artery
HOC: House of Commons
HRA: Health Research Authority
ICU: intensive care unit
JCUH: James Cook University Hospital
MAD: mandibular advancement device
MESA: Multi-Ethnic Study of Atherosclerosis
MVPA: moderate to vigorous-intensity physical activity
NICE: National Institute for Health and Care Excellence
NIHR: National Institute for Health Research
NMA: network meta-analysis
ODI: oxygen desaturation index
OSA: obstructive sleep apnoea
OSAS: obstructive sleep apnoea syndrome
PHE: Public Health England
PPI: public involvement work
PSG: polysomnography
RCT: randomised controlled trial
RFS: rostral fluid shift

ROC: receiver operating characteristic curve
RPE: rating of perceived exertion
SD: standard deviation
SDB: sleep-disordered breathing
SMD: standardised mean difference
SPSS: Statistical Package for the Social Sciences
STHNHSFT: South Tees Hospitals NHS Foundation Trust
SWMS: Specialist weight management services
USMD: unstandardised mean difference
WHO: World Health Organisation

List of Scientific Outputs

Conference presentations:

Suri, S., Batterham, A.M., Ells, L., Danjoux, G. and Atkinson, G.
Association between self-reported walking pace and indicators of sleep-disordered breathing: A population-based investigation. Oral presentation (selected to present in the Young Investigators Award category) at the 19th Annual Congress of the European College of Sport Science in Amsterdam, July 2014 (Conference abstract ID: 265).

Journal articles:

Suri, S.V., Batterham, A.M., Ells, L., Danjoux, G. and Atkinson, G. (2015)
'Cross-sectional association between walking pace and sleep-disordered breathing', *International Journal of Sports Medicine*, 36(10), pp. 843-847.

Atkinson, G., Danjoux, G., Ells, L., **Suri, S.** and Batterham, A.M. (2016)
'Brachial artery diameter, but not flow-mediated dilation, is associated with sleep apnoea in the Multi-Ethnic Study of Atherosclerosis', *Journal of Hypertension*, 34 (3), pp. 410-413.

Abstract

Obstructive sleep apnoea (OSA) is a serious form of sleep-disordered breathing (SDB). OSA is associated with cardiovascular disease, compromises driving safety and increases the risk of peri-surgery complications. Reports suggest that many people with OSA, even those with obesity, remain undiagnosed. Adherence to the treatment of continuous positive airway pressure can be poor. Emerging research points towards an inverse association between physical activity and severity of SDB. Therefore, the work in this thesis involved various studies relevant to the role of physical activity in the diagnosis and treatment of OSA.

In the diagnostic pathway, the first study examined the association between self-reported slow-walking speed (an indicator of frailty) and SDB in the large, cross-sectional Multi-Ethnic Study of Atherosclerosis (MESA). The 95% CI risk differences (multivariable-adjusted) for slow vs. faster walking speed were: sleep apnoea (0.4-2.5%), self-reported apnoeas (0.1-3.8%), loud snoring (1.2-8.3%), and daytime sleepiness (3.0-7.8%). The multivariable-adjusted risk ratio indicated that slower walkers had 1.5 (95% CI: 1.0 to 2.1) times the risk of sleep apnoea vs. faster walkers.

In a second study, which involved weight-loss surgery patients, the body mass index (BMI) item of the STOP-Bang screening tool was replaced with a slow-walking speed item and improved the area under the receiver operating characteristic curve for OSA screening from 0.64 to 0.70. A slower walking speed was also reported significantly more in OSA patients than non-OSA patients (% difference, 95% CI: 21.7%, 4.2-36.5%). This prevalence difference was larger than those observed for any of the STOPANG items. From these studies, it was concluded that a slow-walking speed question might help consolidate screening for OSA.

The first study in the treatment pathway of the thesis was a critical analysis of published evidence syntheses on exercise as a treatment for the symptoms of OSA. It was concluded that, despite some variability between

reviews, especially in meta-analyses (mean AHI reductions between 4.66 and 17.23 events/h reported in RCT-only meta-analyses), exercise has a clinically meaningful effect on reducing OSA severity and daytime sleepiness in adults, independent of BMI changes.

In the context of OSA consequences, the second study conducted in the treatment pathway assessed whether percentage flow-mediated dilation (FMD%), an early indicator of atherosclerosis, is affected by OSA. Using the MESA dataset, it was found that the sex, race and age-adjusted mean FMD% was 0.6% lower in participants with physician-diagnosed sleep apnoea compared to undiagnosed participants. However, this mean difference was 0.3% and not statistically significant when the confounding influence of initial artery diameter was allometrically adjusted for. It was therefore concluded that people with OSA do not demonstrate a clinically important reduction in FMD%. Consequently, this outcome was not included in the final protocol phase of the thesis.

The final chapter in this thesis presents a protocol for a feasibility study examining the benefits of exercise for obese people with OSA who undergo weight-loss surgery. This 12-week aerobic and resistance training protocol was patient-informed and focused on feasibility, safety and acceptability outcomes to inform the design of a subsequent definitive randomised controlled trial. Future work should progress this protocol into the next research phase to support the optimisation of the clinical pathway for weight-loss surgery patients with OSA.

Chapter One: Introduction

1.1 Background and rationale for the research

Obstructive sleep apnoea (OSA) is a severe type of sleep-disordered breathing (SDB), which is characterised by multiple losses of airway patency during sleep (Habib and Phillips, 2007). Prevalence rates of OSA have been reported between three and 17% in the general population (Punjabi, 2008; Peppard *et al.*, 2013) and can be greater than 50% in bariatric groups (Chung, Abdullah and Liao, 2016). This disorder can pose a serious threat to health, increasing the risk of cardiovascular disease and stroke and postoperative complications in undiagnosed patients who undergo surgery (Lattimore, Celermajer and Wilcox, 2003; Chung, Abdullah and Liao, 2016). OSA may also have negative ramifications on an individual's quality of life and daily functioning, compromising occupational and educational performance and driving safety (Stranks and Crowe, 2016).

Importantly, many individuals may be unaware that they have OSA, and reports suggest that a substantial number of people with OSA, even those with obesity, remain formally undiagnosed (Rejon-Parrilla, Garau and Sussex, 2014; Chung, Abdullah and Liao, 2016). Inherent problems in current OSA screening questionnaires (e.g. some questions are reliant on information from a patient's bed partner, if they do have one) may be a potential factor contributing to these poor figures (Nagappa *et al.*, 2017a). Moreover, the 'gold-standard' treatment for OSA, continuous positive airway pressure (CPAP), is not well tolerated by many patients (Rotenberg, Murariu and Pang, 2016). Adherence rates for CPAP remain persistently low over 20 years of data reporting (consistent non-adherence rates of 30-40%) (Rotenberg, Murariu and Pang, 2016). Improved screening and alternative management strategies are undeniably needed to address these problems.

It is well documented that physical activity levels can reduce the risk and severity of multiple diseases (World Health Organisation (WHO), 2018). Over the past decade, a growing body of research has evolved to suggest that physical activity may also have benefits for reducing the severity and symptoms of SDB, independent of changes in body mass index (BMI) (Peppard and Young, 2004; Iftikhar, Kline and Youngstedt, 2014; Simpson *et al.*, 2015; da Silva *et al.*, 2017; Iftikhar *et al.*, 2017; Kline *et al.*, 2017). Therefore, it is plausible to suggest that physical activity could be used to improve the diagnosis and treatment of OSA. However, at present there is a need for further work to expand the evidence base regarding a) the effects of exercise (a sub-category of physical activity) on the severity and symptoms of OSA and b) the mechanisms responsible for the beneficial effects of exercise on the disorder (Iftikhar *et al.*, 2017; WHO, 2018). It is also currently unknown as to how physical activity could be used to improve the screening and diagnosis of OSA.

1.2 Aim and objectives of this thesis

Aim:

To examine the role of physical activity in the diagnosis and treatment of OSA

Objectives:

1. To critically examine published evidence syntheses on exercise as a treatment for OSA
2. To explore whether physical activity-related questions (similar to those on existing OSA screening tools) are:
 - a) Associated with the severity of SDB
 - b) Can be used to improve the diagnostic performance of a current OSA screening questionnaire
3. To undertake work in preparation for designing a protocol for a feasibility randomised controlled trial (RCT) examining the benefits of exercise for patients with OSA:
 - a) Examine the validity of a potential outcome measure for the trial
 - b) Explore OSA patients' views regarding exercise and physical activity
4. To develop a protocol for a feasibility RCT examining the benefits of exercise for patients with OSA

1.3 Structure of this thesis

This thesis consists of nine chapters. There is the introduction to the thesis (chapter one), a chapter about OSA (chapter two), six core chapters (chapters three, four, five, six, seven and eight) and the overall discussion and conclusion (chapter nine). Two of the core chapters (chapters four and six) relate to the screening and diagnosis of OSA, and four of the core chapters (chapters three, five, seven and eight) relate to the treatment of OSA. An overview of the studies, which have been conducted to meet the thesis aim and objectives, is provided in figure 1.1. The diagnostic pathway consists of a cross-sectional study (chapter four), which leads into clinical work (chapter six). The treatment pathway commences with a critical overview of reviews (chapter three), followed by two chapters examining the preparatory work that was undertaken to inform the design of a protocol for a feasibility RCT (chapter five explores a potential outcome measure for this protocol, and chapter seven presents the patient and public involvement (PPI) work that was conducted to inform the trial design). The protocol for the feasibility RCT is presented in chapter eight.

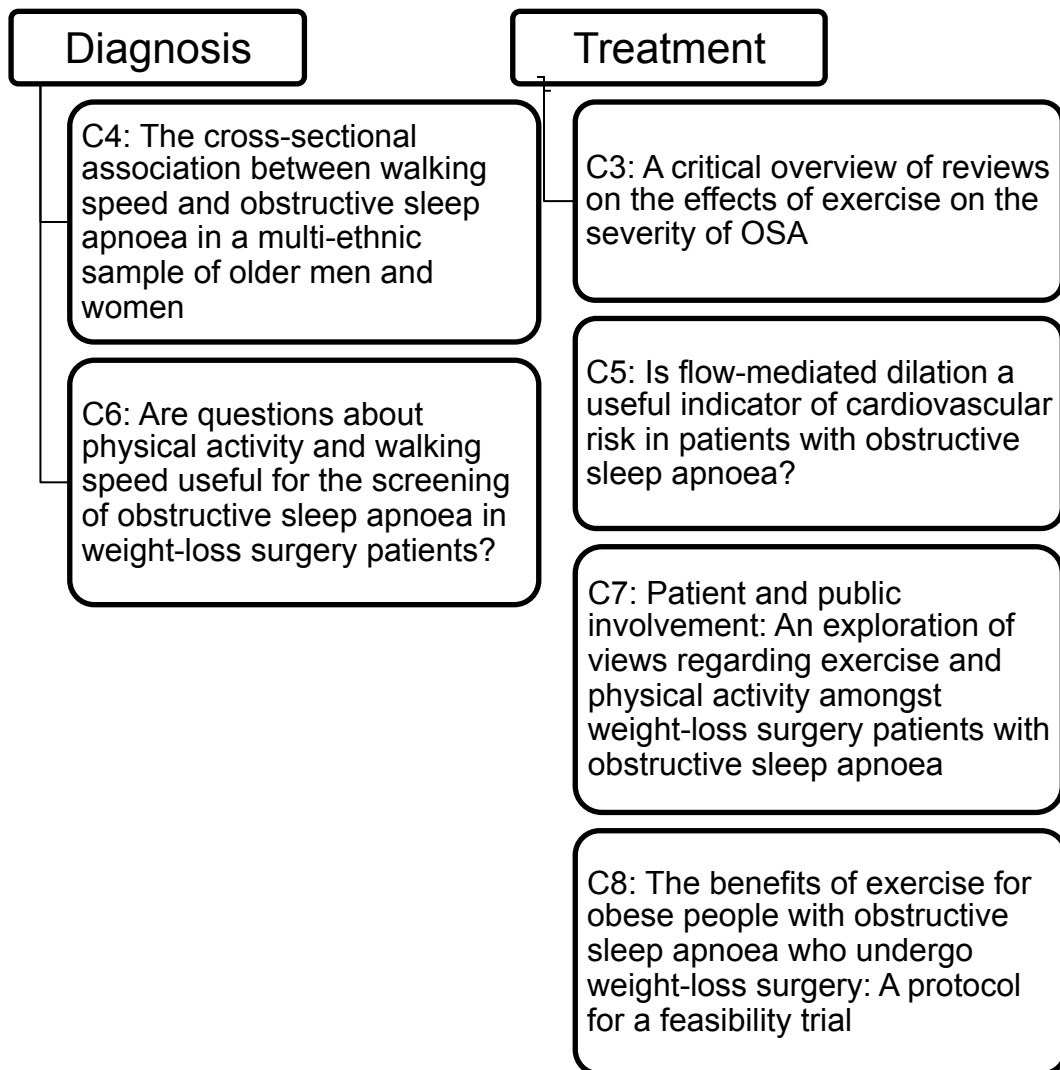


Figure 1.1: The structure of this thesis (C = Chapter)

Chapter Two: Obstructive Sleep Apnoea (OSA)

2.1 What is OSA?

2.1.1 Overview of OSA

Obstructed breathing encompasses a continuous spectrum of severity ranging from loud snoring to physician-diagnosed severe OSA (Habib and Phillips, 2007). OSA is one of the most serious sleep-related breathing disorders and is characterised by multiple losses of airway patency during sleep, resulting in partial (hypopnoea) and/or full (apnoea) airway obstruction (Habib and Phillips, 2007; Aron *et al.*, 2009) (Figure 2.1). The severity of OSA is classified from mild to severe using the apnoea-hypopnoea index (AHI), which is the average number of apnoea (airflow is blocked for ≥ 10 seconds) and hypopnoea (airflow reduction of $> 50\%$ for ≥ 10 seconds) episodes per hour during sleep (Danjoux and Habgood, 2016; NHS, 2016) (Table 2.1). When accompanied by excessive daytime sleepiness, OSA is called OSA syndrome (OSAS) (Danjoux and Habgood, 2016).

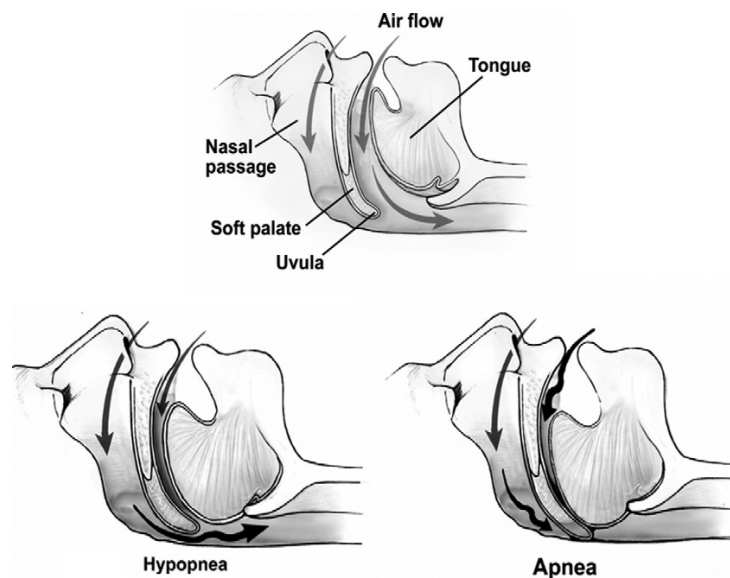


Figure 2.1: Partial and full airway obstruction (Obtained from Somers *et al.*, 2008)

Table 2.1: Severity classification of OSA using the apnoea-hypopnoea index (AHI) (NHS, 2016)

OSA severity classification	AHI
	(Average number of apnoeas/hypopnoeas per hour of sleep)
Mild	5 to 14
Moderate	15 to 30
Severe	> 30

The prevalence of OSA in the general adult population is reported to be between three and 17%, with men and older individuals bearing a greater risk for the disorder (Punjabi, 2008; Peppard *et al.*, 2013). Much higher prevalence rates of between 50 and 70% have been reported in severely obese populations (Riad and Chung, 2013; Chung, Abdullah and Liao, 2016). However, as stated in chapter one, reports suggest that a substantial number of people with OSA, even those with obesity, remain formally undiagnosed (Rejon-Parrilla, Garau and Sussex, 2014; Chung, Abdullah and Liao, 2016).

Symptoms of the disorder include loud snoring, witnessed breathing pauses during sleep and excessive daytime sleepiness (Punjabi, 2008). Factors that increase the risk of OSA include obesity, large neck size (> 40cm), male gender, advancing age, craniofacial abnormalities (e.g. micrognathia, acromegaly), enlarged tonsils and behaviours such as cigarette smoking and alcohol use (Punjabi, 2008; Danjoux and Habgood, 2016).

2.1.2 Anatomy and pathophysiology of OSA

The upper airway can be divided into four anatomical subsections; the nasopharynx, the velopharynx (or retropalatal oropharynx, located between

the hard palate and the soft palate), the oropharynx and the hypopharynx (Ayappa and Rapoport, 2003; Fogel, Malhotra and White, 2004) (Figure 2.2). The pharyngeal airway is a complex structure, which gives rise to our ability for speech and vital functions such as respiration and swallowing (Fogel, Malhotra and White, 2004). The pharynx has evolved to accommodate these competing functions by sacrificing rigid support of the hyoid bone, a central anchoring point for the tongue muscles (Ramar and Guilleminault, 2007). Therefore, the upper airway is susceptible to collapse and relies largely on muscle activity to maintain airway patency (collapse usually occurs in the velopharynx or oropharynx or both) (Ayappa and Rapoport, 2003; Fogel, Malhotra and White, 2004; Ramar and Guilleminault, 2007). The size of the upper airway depends on the balance between forces that would collapse the airway such as negative intraluminal pressure and increased tissue (extraluminal) pressure, and forces that maintain airway patency (e.g. contraction of the genioglossus, a pharyngeal dilator muscle) (Fogel, Malhotra and White, 2004).

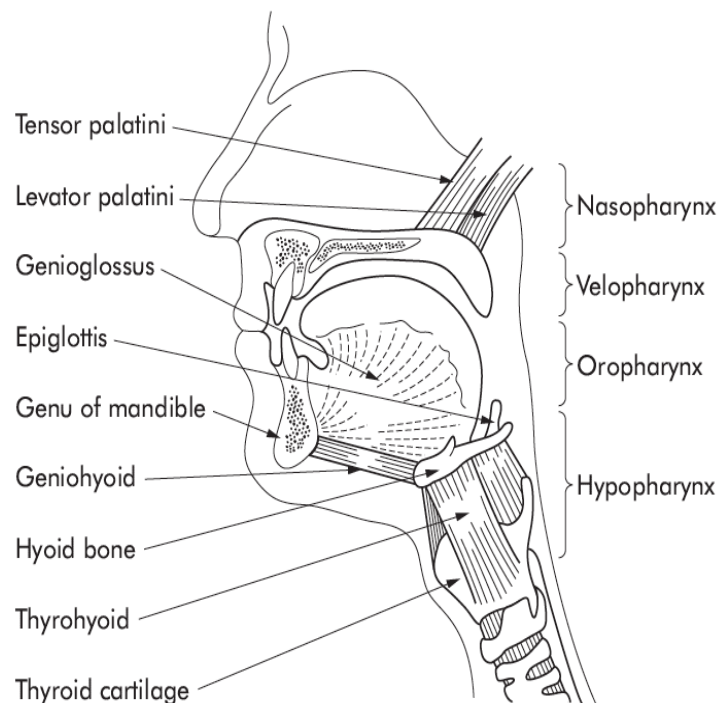


Figure 2.2: Anatomy of the upper airway (Obtained from Fogel, Malhotra and White, 2004)

A number of theories have been proposed to explain the pathogenesis of OSA, and it is thought that different factors contribute to the development and severity of the disorder in different individuals (Nguyen, Yim and Malhotra, 2007). However, the predominant theory of pathogenesis pertains to an anatomically small or more collapsible airway (e.g. due to increased fat deposition around the airway) in combination with a sleep-induced fall in upper airway muscle activity (Fogel, Malhotra and White, 2004; Danjoux and Habgood, 2016). It is believed that increased activity of the upper airway dilator muscles during wakefulness compensates for any predisposition to airway collapse (Nguyen, Yim and Malhotra, 2007). However, these neuromuscular compensatory mechanisms are lost during sleep and leave certain individuals susceptible to apnoeic events (Danjoux and Habgood, 2016). Arousal from sleep is needed to restore airway patency (resumption of breathing occurs with arousals secondary to an increase in oropharyngeal dilator muscle tone) (Fogel, Malhotra and White, 2004; Danjoux and Habgood, 2016). The consequence of this repetitive cycle and associated hypoxemia and hypercapnia is a highly disrupted sleep period, which can be detrimental to an individual's health and daily functioning (Fogel, Malhotra and White, 2004; Somers *et al.*, 2008).

2.2 Potential consequences of OSA

The recurrent apnoeas/hypopnoeas characteristic of OSA lead to repetitive episodes of intermittent hypoxemia, intrathoracic pressure changes and arousals, which can activate a number of harmful disease mechanisms (e.g. oxidative stress, sympathetic activation, systemic inflammation, metabolic dysfunction, endothelial dysfunction) (Somers *et al.*, 2008; Dewan, Nieto and Somers, 2015) (Figure 2.3). It is perhaps not surprising to learn that OSA is linked to serious health conditions (Rejon-Parrilla, Garau and Sussex, 2014).

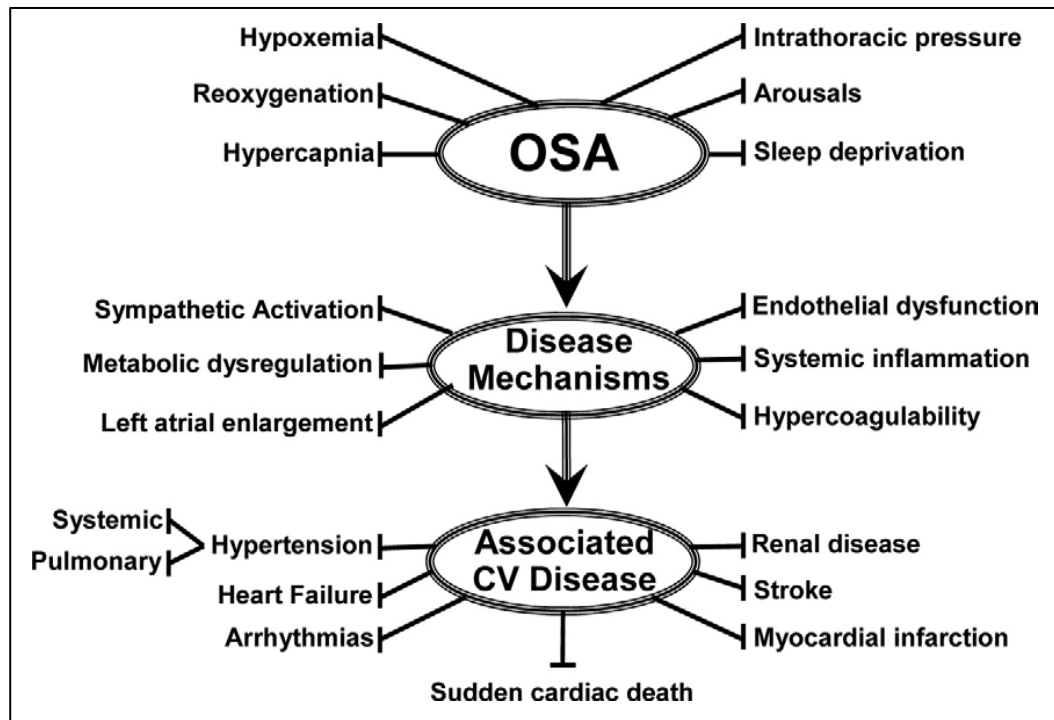


Figure 2.3: Potential pathophysiological components of OSA, activation of disease mechanisms and development of cardiovascular disease (CV = cardiovascular) (Obtained from Somers *et al.*, 2008)

In particular, there is evidence to suggest a strong association between OSA and vascular diseases (Budhiraja and Quan, 2007; Yeboah *et al.*, 2011; Yacoub *et al.*, 2017; Ryan, 2018; Tietjens *et al.*, 2019), and reports indicate a prevalence of OSA between 30 and 60% in patients with hypertension, heart disease and stroke (Lattimore, Celermajor and Wilcox, 2003). Moreover, Redline *et al.*, (2010) reported that moderate to severe levels of OSA were associated with an approximately three-fold increased risk of ischemic stroke in men in The Sleep Heart Health Study. In a meta-analysis of prospective cohort studies examining the association of OSA with the risk of vascular outcomes and mortality, Xie *et al.*, (2017) reported that moderate and severe OSA were associated with significantly increased risks of major adverse cardiac events and coronary heart disease. These latter authors also reported that this relationship might differ by sex (Xie *et al.*, 2017).

The substantial evidence base linking SDB and vascular problems has led to the inclusion of an item for hypertension being included on a well-recognised OSA screening tool (the STOP-Bang questionnaire) (Chung, Abdullah and Liao, 2016) and also brought to light the importance of considering OSA in certain vascular disorders such as resistant hypertension (Tietjens *et al.*, 2019). Although work is needed to further investigate sex differences and confirm and establish causality, the research certainly highlights the importance of early diagnosis and treatment in order to reduce the damaging physiological effects of OSA on the vascular system (Budhiraja and Quan, 2007; Tietjens *et al.*, 2019). It is also evident from the research that any strategy for treating OSA should include outcomes pertaining to these vascular consequences. One such outcome could be the percentage flow-mediated dilation of the brachial artery (FMD%), which is suggested to be an early indicator of cardiovascular disease that is reduced in people with OSA (Ali *et al.*, 2014; Hoyos *et al.*, 2015).

In addition to compromising physical health, OSA can also impact upon an individual's cognitive function, leading to detrimental consequences for occupational and educational functioning and driving safety (Stranks and Crowe, 2016). In a recent meta-analysis, Stranks and Crowe (2016) evaluated the effects of OSA on cognitive function (assessed using objective neuropsychological measures). They reported that the greatest deficits were found in the areas of psychomotor speed and executive function, with memory functions, motor control, construction, attention and speed of processing abilities affected to a lesser extent (Stranks and Crowe, 2016). Excessive daytime sleepiness, a key symptom of OSAS, can further compound the ability to be effective and perform optimally in daily life (Johns, 1993). Given the functionally limiting nature of the disorder, it is perhaps unsurprising that OSA has been associated with disturbances in mood and a poor health-related quality of life (Lacasse, Godbout and Series, 2002; Pichel *et al.*, 2004; Lee *et al.*, 2016). These combined physical, psychological and functional consequences of OSA can be devastating for the individual and their family members and place strain on economic resources (Rejon-Parrilla, Garau and Sussex, 2014).

The societal and economic costs of OSA are substantial, and reports indicate that OSA patients have a significantly increased risk of motor vehicle crashes, consume extra health-care resources and may be more likely to suffer from work-related injuries and work disability (including absenteeism) (Hirsch, Bansback and Ayas, 2015). It is particularly concerning to consider that these costs may escalate in the future given the current obesity problem (Reed, Pengo and Steier, 2016). Further, as people are now living longer, the OSA risk factor of age becomes a potential issue that could also augment OSA-related economic costs (Rejon-Parrilla, Garau and Sussex, 2014). A current health economics report suggests that increasing diagnosis and treatment of the disorder could result in worthwhile economic gain for the UK (e.g. by increasing workplace productivity and decreasing NHS spending on road-traffic accidents and OSA-related comorbidities such as vascular diseases) (Rejon-Parrilla, Garau and Sussex, 2014). Therefore, it is clear that increasing the diagnosis and treatment of OSA is of paramount importance to the nation and should be prioritised to a) improve the lives of individual sufferers and their families and b) reduce strain on already compromised economic and health-care systems.

2.3 The diagnosis of OSA

Early diagnosis of disease is a key aim of current healthcare policy (Public Health England (PHE), 2016). Prompt diagnosis of disease can facilitate treatment and potentially alter the course of a person's life. The diagnostic process for OSA involves the use of screening tools (e.g. STOP-Bang questionnaire) followed by more extensive testing in the person's home (e.g. overnight pulse oximetry) or a clinical environment (overnight polysomnography or PSG) in conjunction with patient history and clinical examination (Danjoux and Habgood, 2016). The following sections describe these tools and tests in greater detail.

2.3.1 Polysomnography

The 'gold standard' diagnostic test for OSA is supervised in-laboratory overnight polysomnography (PSG) (Kapur *et al.*, 2017). During PSG, multiple physiologic signals are recorded and monitored while a person sleeps, including brain waves (electroencephalogram, EEG), air flow from the nose and mouth, chest and abdominal movements, heart rate and rhythm (electrocardiogram, ECG) and blood oxygen levels (oximetry) (Division of Sleep Medicine - Harvard Medical School, 2011) (Figure 2.4). Diagnosis and severity of OSA (mild, moderate or severe) is made by a sleep specialist and is based on the history and severity of presenting symptoms and the AHI (as evaluated from the PSG) (National Institute for Health and Care Excellence (NICE), 2008; Danjoux and Habgood, 2016) (Table 2.1). Yet, PSG is time consuming, labour intensive, costly and may not always be available in the immediate vicinity (Nagappa *et al.*, 2015). Therefore, high quality home-based sleep apnoea testing (e.g. overnight pulse oximetry measuring parameters such as the oxygen desaturation index, ODI) is accepted as suitable in conjunction with the patient's history and severity of presenting symptoms for diagnosing OSA (NICE, 2008; Danjoux and Habgood, 2016; Kapur *et al.*, 2017). However, guidelines strongly indicate that complex (e.g. where a patient has significant comorbidities) and unclear cases should still be assessed with full PSG (Kapur *et al.*, 2017).

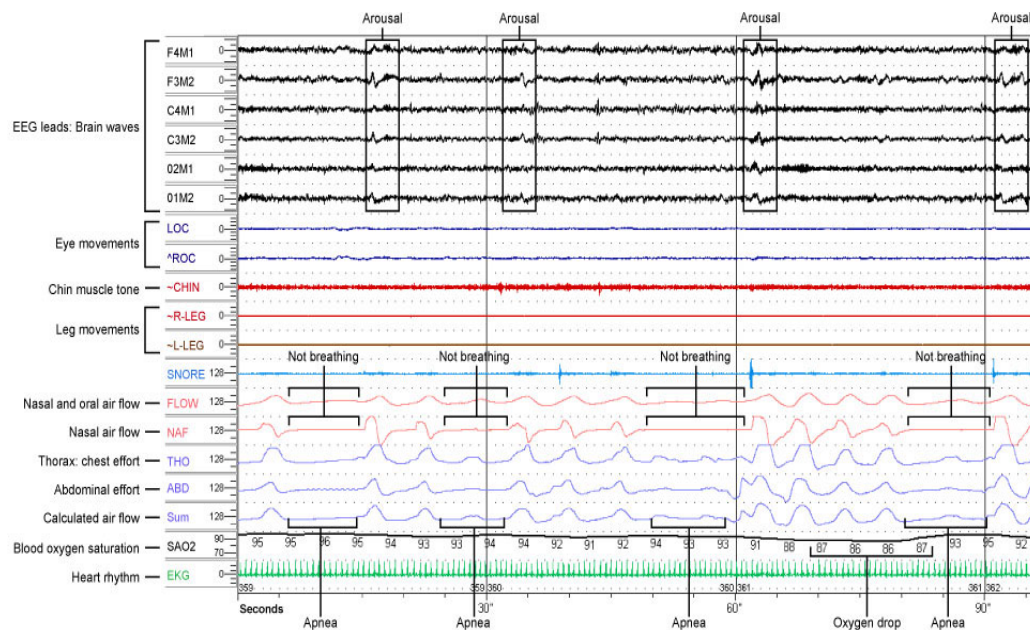


Figure 2.4: Polysomnogram highlighting the repeated breathing pauses (apnoeas) that happen in a person with OSA (EEG = electroencephalogram) (Obtained from the Division of Sleep Medicine - Harvard Medical School, 2011)

2.3.2 Screening tools

Due to the extra time and resources needed for more in-depth OSA testing, a number of screening tools (e.g. the STOP, STOP-Bang and Berlin questionnaires) have been developed to help identify individuals who have a greater risk of OSA and require further evaluation (Danjoux and Habgood, 2016). NB: The American Academy of Sleep Medicine (AASM) strongly recommend that these self-report tools should not be used to make any final OSA diagnoses and employed for screening purposes only (Kapur *et al.*, 2017).

The STOP (snoring, daytime tiredness, observed apnoeas and high blood pressure) and STOP-Bang (snoring, daytime tiredness, observed apnoeas, high blood pressure - BMI, age, neck circumference and gender) questionnaires were developed and validated in surgical patients to facilitate

the need for a quick, simple and concise screening tool for OSA (Chung *et al.*, 2008; Chung *et al.*, 2012; Chung *et al.*, 2014; Chung, Abdullah and Liao, 2016). The most widely used questionnaire, the STOP-Bang, consists of eight 'yes/no' questions related to risk factors and indicators of OSA as abbreviated in the acronym (Chung, Abdullah and Liao, 2016) (Figure 2.5; Appendix one). Each item is scored one point for a response of 'yes' and zero points for a response of 'no', and a final score is calculated between 0-8 points (Chung, Abdullah and Liao, 2016). For the general population, scores of 0-2 indicate a low risk of OSA, scores of 3-4 indicate an intermediate risk of OSA and scores of 5-8 indicate a high risk of OSA (patients can also be classified as higher risk of OSA if they answer 'yes' to two of the STOP items + 'yes' to gender, age or neck circumference items) (Chung, Abdullah and Liao, 2016). The STOP-Bang score is currently used clinically to stratify and triage patients for extended testing (Danjoux and Habgood, 2016).

STOP-Bang Questionnaire

1. **S**noring: Do you snore loudly (loud enough to be heard through closed doors)?
Yes No
2. **T**ired: Do you often feel tired, fatigued, or sleepy during daytime?
Yes No
3. **O**bserved: Has anyone observed you stop breathing during your sleep?
Yes No
4. **B**lood *P*ressure: Do you have or are you being treated for high blood pressure?
Yes No
5. **B**MI: BMI more than 35 kg/m²?
Yes No
6. **A**ge: Age over 50 years old?
Yes No
7. **N**eck circumference: Neck circumference greater than 40 cm?
Yes No
8. **G**ender: Male?
Yes No

Figure 2.5: The STOP-Bang questionnaire (Obtained from Chung *et al.*, 2014)

Other OSA screening tools have also been developed, including the Berlin Questionnaire (BQ), which was designed to screen for OSA in primary care (Netzer *et al.*, 1999). This questionnaire is comprised of three main categories pertaining to a) snoring and apnoeas during sleep, b) daytime sleepiness and c) blood pressure and obesity (Pataka *et al.*, 2014). A patient's score is used to stratify them as being low or high risk of OSA (Pataka *et al.*, 2014; Miller and Berger, 2016). The Epworth Sleepiness Scale (ESS) is a validated questionnaire for assessing sleepiness in order to identify individuals with excessive daytime sleepiness (Johns, 1991; Johns, 1993) (Figure 2.6; Appendix two). This self-administered questionnaire consists of eight questions asking about an individual's propensity to fall asleep or doze in a number of routine daily activities, e.g. when watching TV or sitting and talking to someone (Johns, 1991). The chance of dozing (on a scale from 0-3) is recorded for each of the eight questions, and a final score is calculated out of 24 (Johns, 1993). A score of ≥ 12 on the ESS has been highlighted as strongly suggestive of increased daytime somnolence (Danjoux and Habgood, 2016).

THE EPWORTH SLEEPINESS SCALE

Name: _____

Today's date: _____ Your age (years): _____

Your sex (male = M; female = F): _____

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently try to work out how they would have affected you. Use the following scale to choose the *most appropriate number* for each situation:

- 0 = would *never* doze
- 1 = *slight* chance of dozing
- 2 = *moderate* chance of dozing
- 3 = *high* chance of dozing

Situation	Chance of dozing
Sitting and reading	_____
Watching TV	_____
Sitting, inactive in a public place (e.g. a theater or a meeting)	_____
As a passenger in a car for an hour without a break	_____
Lying down to rest in the afternoon when circumstances permit	_____
Sitting and talking to someone	_____
Sitting quietly after a lunch without alcohol	_____
In a car, while stopped for a few minutes in the traffic	_____

Thank you for your cooperation

Figure 2.6: The Epworth Sleepiness Scale (Obtained from Johns, 1991)

A number of studies have been conducted to compare the diagnostic performance of the STOP, STOP-Bang, BQ and the ESS (Cowan *et al.*, 2014; Pataka *et al.*, 2014; Chiu *et al.*, 2017). Cowan *et al.*, (2014) found that the STOP-Bang questionnaire had superior predictive performance compared to the STOP and Berlin questionnaires at both cut-points $AHI \geq 5$ and $AHI \geq 15$ in a sleep clinic in Glasgow. Pataka *et al.*, (2014) evaluated five different questionnaires for assessing sleep apnoea syndrome in a single-centre analysis in Greece. They found that the STOP-Bang questionnaire had the highest sensitivity (97.6%), largest area under the receiver operating characteristic curve (AUC) (0.73, 95% confidence interval (CI), 0.7-0.76) and best odds ratio (5.9, 95% CI, 3.6-9.5), but the lowest specificity (12.7%) for $AHI \geq 15$. In a bivariate meta-analysis, Chiu *et al.*, (2017) found that the STOP-Bang questionnaire was a more accurate tool for detecting mild, moderate and severe OSA (sensitivity: mild = 88%, moderate = 90% and severe = 93%) when compared against the STOP tool, BQ and ESS. However, the STOP-Bang evidenced poor specificity results for all OSA severities (mild = 42%, moderate = 36% and severe = 35%) (Chiu *et al.*, 2017). These findings appear robust across the diverse studies reviewed and indicate that although the STOP-Bang tool may perform well for OSA detection, its poor specificity is a limitation, which could lead to high false-positive rates and unnecessary referrals to already struggling NHS services (Chung, Abdullah and Liao, 2016). Future work needs to examine how to improve the specificity of this promising screening tool.

2.4 The treatment of OSA

The fundamental aims of OSA treatment are to reduce, and preferably eliminate, nocturnal apnoeic events and decrease the severity of OSA symptoms (NICE, 2008; Spicuzza, Caruso and Maria, 2015). Appropriate treatment can also alter the physiological and metabolic consequences of OSA and potentially increase an individual's lifespan (Deacon *et al.*, 2016). Several treatment options have been proposed to manage the disorder, including CPAP, mandibular advancement devices (MADs), upper airway surgery, hypoglossal nerve stimulation, weight loss/lifestyle management

strategies, positional therapies and pharmacological interventions (Deacon *et al.*, 2016). Currently, the 'gold standard' treatment is CPAP for moderate/severe OSA (with weight loss alongside for those who are overweight/obese) and lifestyle advice/MADs for mild OSA (NICE, 2008; Danjoux and Habgood, 2016).

2.4.1 CPAP, MADs and weight loss

CPAP uses positive pressure to splint the upper airway open during sleep (NICE, 2008). The CPAP device consists of a unit that generates airflow, which is directed to the airway via a mask worn at night (NICE, 2008). The pressurised air acts to splint the upper airway open and prevents it from collapsing (Sutherland, Phillips and Cistulli, 2015). Different CPAP devices (e.g. fixed or auto-titrating CPAP) are available and need to be chosen and fitted with a clinical specialist (NICE, 2008). Oral appliances are the leading alternative to CPAP (Sutherland, Phillips and Cistulli, 2015). Oral appliances such as MADs reposition the tongue and/or lower jaw to increase the dimensions of the airway lumen, reducing airway collapsibility (Phillips *et al.*, 2013).

CPAP has shown to be effective in treating OSA and can eliminate/reduce obstructive events, improve quality of life and decrease daytime sleepiness (Phillips *et al.*, 2013; Deacon *et al.*, 2016; Sharples *et al.*, 2016). The research suggests that MADs are also effective in the treatment of OSA, yet approximately 40% of patients using these devices still exhibit a clinically elevated AHI (Phillips *et al.*, 2013; Deacon *et al.*, 2016; Sharples *et al.*, 2016). A randomised crossover trial (Phillips *et al.*, 2013), meta-analysis of randomised controlled trials (RCTs) (Sharples *et al.*, 2016) and a recent network meta-analysis (NMA) (Iftikhar *et al.*, 2017) all provided evidence to suggest that CPAP is superior to MADs for improving the AHI in adults with OSA. However, these studies were predominantly on men with moderate to severe OSA. Therefore, interpretations may not generalise to all OSA patients. On other outcomes, such as sleepiness and quality of life, CPAP

and MADs show similar improvements (Philips *et al.*, 2013; Sutherland, Phillips and Cistulli, 2015; Iftikhar *et al.*, 2017).

Despite the superior performance of CPAP for OSA severity reduction, adherence to the treatment is a major concern. Adherence rates remain persistently low over 20 years of data reporting (consistent non-adherence rates of between 30 and 40%) (Rotenberg, Murariu and Pang, 2016). Common complaints influencing disuse have been highlighted as dry nose and mouth, general discomfort and perceived negative social impact (NICE, 2008; Deacon *et al.*, 2016). While MADs also have side effects (e.g. tooth and jaw pain and hypersalivation) and are not suitable for all individuals, they do have higher adherence rates, e.g. > 75% (Sutherland, Phillips and Cistulli, 2015; Deacon *et al.*, 2016). Such poor CPAP compliance rates have even brought into question whether CPAP should still be accepted as the 'gold-standard' of treatment for OSA, as high efficacy but low compliance could ultimately undermine overall treatment effectiveness (Rotenberg, Murariu and Pang, 2016; Basyuni, Barabas and Quinnell, 2018). Future research is needed to examine this issue further.

Weight loss treatments are commonly used in the management of OSA. Increased tissue pressure due to fat deposition in the upper airway can magnify the chance of pharyngeal collapse (Joosten, Hamilton and Naughton, 2017). Further, greater fat deposition in the chest and abdominal regions can affect lung volumes and impact negatively on the disorder (Joosten, Hamilton and Naughton, 2017). In a longitudinal study of weight change and SDB, Peppard *et al.*, (2000) found that a 10% weight gain predicted an approximately 32% increase in AHI and a 10% weight loss predicted a 26% decrease in AHI. Moreover, a recent meta-analysis of RCTs found that weight loss through lifestyle interventions (largely diet-focused) resulted in a reduction in weight (mean difference -13.76 kg, 95% CI, -19.21 to -8.32) and OSA severity (mean difference -16.09 events/h, 95% CI, -25.64 to -6.54) (Mitchell *et al.*, 2014). However, the high heterogeneity in the summary effect for AHI ($I^2 = 92.2\%$) and predominance of data from men in the studies they analysed makes it difficult to draw firm conclusions from this

work that can be generalised to the wider OSA population (Mitchell *et al.*, 2014). In a current NMA examining the effect of different interventions (e.g. CPAP, MADs) on OSA, Iftikhar *et al.*, (2017) concluded that dietary weight loss, although not negligible, was the least effective for reducing the AHI (mean treatment effect -12.27 events/h, 95% CI, -18.79 to -5.75). The research presented, despite limitations, does indicate that weight loss has a role to play in OSA therapy. However, to concur with Joosten, Hamilton and Naughton's (2017) conclusions from their narrative overview on the impact of weight loss for the management of OSA, weight loss may not be a cure for all sufferers and most likely is a beneficial adjunctive therapy, especially in obesity-related moderate to severe OSA.

Drawing conclusions on OSA treatment, the most efficacious therapy option is undoubtedly CPAP. However, poor adherence rates may offset its beneficial effects. MADs are a promising choice, yet are not suitable for all individuals and still leave residual OSA. Weight loss shows promise as an adjunctive therapy, but is unlikely to lead to a cure, especially in more severe forms of the disorder. Overall, while these treatment options are encouraging, there is still a need to investigate different therapy modalities for this life-altering disorder.

2.5 Physical activity and OSA

It is widely accepted that physical activity is important for disease prevention (WHO, 2018). Over the past decade, an emerging body of research has evolved to suggest that physical activity may have benefits for reducing the severity and symptoms of OSA (Peppard and Young, 2004; Simpson *et al.*, 2015; da Silva *et al.*, 2017; Kline *et al.*, 2017). In their early work, Peppard and Young (2004) measured the association between exercise and SDB in participants enrolled in the Wisconsin Sleep Cohort Study (N = 1104) and reported a statistically significant trend between decreasing mean AHI and increasing hours of weekly exercise. Interestingly, the authors observed that this association persisted even after accounting for measures of body habitus (Peppard and Young, 2004). Encouragingly, more recent studies

have all evidenced results in-line with this research. Simpson *et al.*, (2015) found that in comparison with moderate exercise, the high, low and nil exercise groups in their case-control study had an odds ratio for moderate-severe OSA of 0.6 (95% CI, 0.5-0.8), 1.6 (95% CI, 1.2-2.0) and 2.7 (95% CI, 1.9-3.7) respectively. Further, in a large population-based study (N = 5453), da Silva *et al.*, (2017) observed that exercise was significantly associated with lower odds for moderate and severe OSA. Finally, Kline *et al.*, (2017) examined the associations of sedentary time and moderate to vigorous-intensity physical activity (MVPA) with SDB and polysomnographic sleep in community-dwelling adults and concluded that high sedentary time and low MVPA, and especially their combination, were associated with higher AHI values. BMI was adjusted for in all three of these studies (Simpson *et al.*, 2015; da Silva *et al.*, 2017; Kline *et al.*, 2017).

As a whole, these intriguing findings certainly appear to support the proposal that being less physically active independently increases the risk and severity of OSA. Therefore, interventions that involve increasing physical activity levels may provide a much-needed alternative treatment avenue for OSA patients. Although the results so far are promising, the predominant cross-sectional nature of the research reviewed limits the ability to make any definitive inferences about causality, and while PSG was used to assess sleep across all of the studies, physical activity was unanimously self-reported. Self-reported and objectively assessed measures of MVPA and sedentary time have shown to be only modestly correlated, so it is possible that the data collected may not reflect participants' 'true' activity levels (Kline *et al.*, 2017). So, before advancing further with the thesis it is important to examine whether these results are supported by higher-level evidence in RCTs. Consequently, chapter three presents a critical overview of reviews on the effects of exercise on the severity of OSA. Before moving to this chapter, the potential mechanisms explaining the effect of increased physical activity on OSA will be discussed.

2.5.1 Physical activity-related mechanisms and OSA

It is commonly assumed that increased physical activity leads to a reduction in BMI (an important risk factor for OSA), which in turn reduces OSA severity (Peppard and Young, 2004). However, the independent associations between increased physical activity and a reduced severity of OSA reported in the studies reviewed indicate that there are other ‘activity-related’ or ‘exercise-specific’ mechanisms accounting for these reductions. The most discussed mechanism pertains to the nocturnal ‘rostral fluid shift’ (RFS) (Redolfi *et al.*, 2009). The RFS hypothesis proposes that sedentary living can lead to increased fluid accumulation in the legs during the daytime (reduced activity of the skeletal-muscle pump), which shifts to the rostrum (towards the head) when lying supine to sleep, increasing tissue pressure and the propensity for upper airway collapse (Redolfi *et al.*, 2009; Kline *et al.*, 2017) (Figure 2.7). Redolfi *et al.*, (2009) tested the hypothesis that the AHI during sleep would be related to the amount of fluid displaced from the legs overnight and that this in turn would be related to the time spent sitting the previous day. In support of the RFS, these authors found that in 23 non-obese healthy men, the overnight change in leg fluid volume was strongly correlated with the AHI ($r = -0.773$, $p < 0.001$), the change in neck circumference ($r = -0.792$, $p < 0.001$) and the time spent sitting ($r = -0.588$, $p = 0.003$).

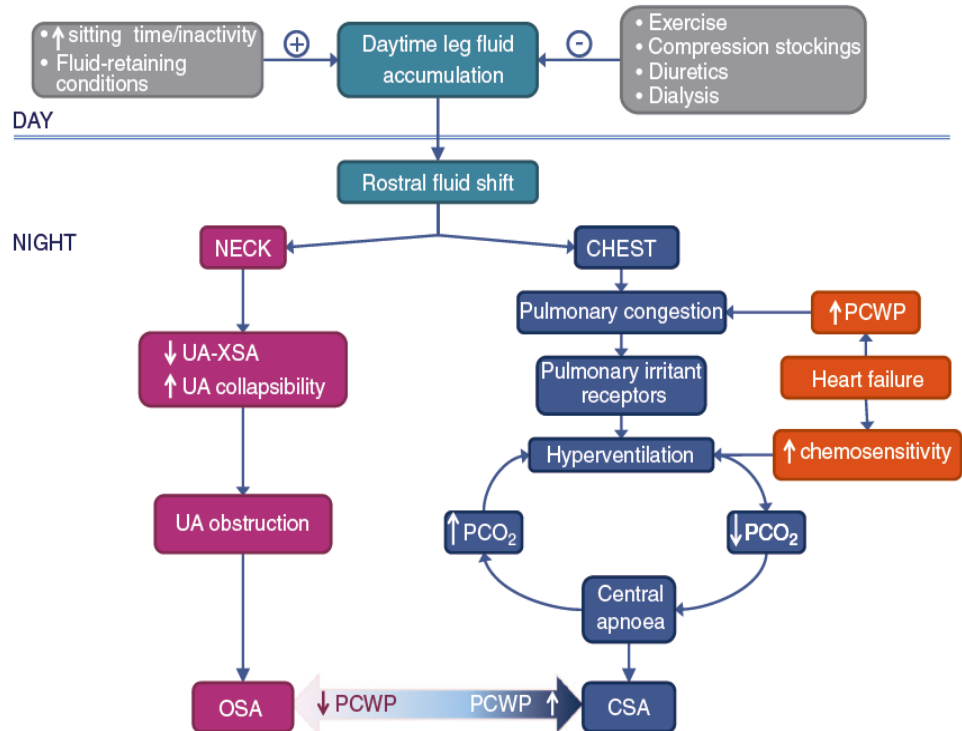


Figure 2.7: The Rostral Fluid Shift: Daytime fluid accumulation in the lower-extremities can shift to the neck and lungs in the supine sleeping position. Fluid shifting to the neck may increase tissue pressure and cause the upper airway to narrow, predisposing to OSA. Fluid shifting to the lungs may provoke hyperventilation, predisposing to central sleep apnoea (White and Bradley, 2013). CSA, central sleep apnoea; PCO_2 , partial pressure of carbon dioxide; PCWP, pulmonary capillary wedge pressure; UA, upper airway; UA-XSA, upper airway cross-sectional area. Figure obtained from White and Bradley (2013)

Higher-level evidence also supports the rostral shift mechanism (Redolfi *et al.*, 2015; Mendelson *et al.*, 2016). Mendelson *et al.*, (2016) examined the effects of a 4-week walking intervention (30 minutes walking five days per week) on the severity of SDB and the nocturnal RFS in a RCT of 34 adults with coronary artery disease (CAD) and moderate to severe SDB. These authors found that the exercise group experienced a significantly greater decrease in the AHI compared to the control group, in association with a greater reduction in the overnight change in leg fluid volume (Mendelson *et al.*, 2016). These reductions were also accompanied by an increase in the

overnight change in upper-airway cross-sectional area in the exercise group and occurred in the absence of any weight loss (Mendelson *et al.*, 2016).

In a randomised crossover trial, Redolfi *et al.*, (2015) found that a one-week walking intervention (two walking sessions per day, 45 minutes per session) resulted in an AHI reduction of 30% with a concomitant reduction in the amount of fluid shifting from the legs to the neck overnight in eight sedentary non-severely obese participants with moderate to severe OSA. However, there are limitations to the research. The predominance of male participants and fact that one study assessed patients with CAD reduces the ability to generalise from the results to females and other population groups. Also, these latter two studies employed a walking intervention, which again reduces the ability to generalise from the work to other modes of exercise. Future research is needed to explore the effect of walking interventions on the RFS in more diverse sample groups. As Kline (2016) suggests, this work should adopt walking protocols similar to Mendelson *et al.*'s (2016), which was more realistic and in-line with current exercise recommendations than Redolfi *et al.*'s (2015) regimen. Further work should also explore the effect of different exercise modalities on the RFS (Kline, 2016).

It is uncertain at present as to whether reductions in AHI due to exercise are an acute effect related solely to the RFS or whether exercise leads to additional adaptations that contribute to AHI reduction alongside the RFS (Kline *et al.*, 2016; Mendelson *et al.*, 2016). While the research is certainly promising regarding the RFS, there is also evidence to indicate that other mechanisms may be contributing to the reductions in OSA severity (Kline, 2016). Kline (2016) highlights that in one of his group's research studies examining the effects of a 12-week exercise intervention on OSA (Kline *et al.*, 2011), post-intervention assessment of SDB severity was conducted following a day where the participants had not exercised. Kline (2016) suggests that the 24% reduction in the AHI observed in this study is unlikely to be attributable to the RFS if it is an acute training effect. Other mechanisms to explain these independent effects of exercise on SDB have been proposed in the literature and include increased respiratory stability

through more consolidated and deeper sleep, increased strength and fatigue resistance of the upper airway dilators and decreased nasal resistance (Kline *et al.*, 2011; Kline, 2016). However, as Kline (2016, p. 24) states, “to date, these mechanisms have been inadequately tested and remain largely speculative”.

To conclude, there is a growing body of evidence to support the RFS hypothesis, yet further research is needed using larger sample sizes and more diverse populations and exercise modalities. Further research is also needed to explore the other mechanisms discussed. This work could improve understanding of the pathogenesis of OSA and help inform future management of the disorder (Mirrakhimov, 2013).

Chapter Three: A critical overview of reviews on the effects of exercise on the severity of OSA

3.1 Introduction

Sleep is a fundamental requirement for optimal everyday functioning and is an essential component of human life (Kline *et al.*, 2017). As discussed in chapter two, disruptions to this vital behaviour can lead to negative consequences for the individual, society and wider economy (Rotenberg, Murariu and Pang, 2016). Poor adherence to the ‘gold-standard’ treatment for OSA, namely CPAP, has led to increased interest in alternative methods of therapy to reduce daytime sleepiness, normalise sleep architecture and improve numerous health-specific outcomes (Rotenberg, Murariu and Pang, 2016).

The possible utility of physical activity as a treatment for OSA has been proposed in recent years after observing positive associations between being more physically active and a reduced incidence of SDB (Peppard and Young, 2004; Awad *et al.*, 2012; Simpson *et al.*, 2015; Kline *et al.*, 2017). Similar results in RCTs examining the effects of exercise on OSA have sparked interest among researchers, especially since OSA severity reduction has occurred despite minimal/no weight loss (Kline *et al.*, 2011; Sengul *et al.*, 2011). Encouragingly, the current evidence-base does appear to indicate that there is an ‘exercise-specific’ pathway for improving OSA.

In order to synthesise this body of research, a number of reviews examining the effects of exercise on OSA have been conducted over the past five years (Araghi *et al.*, 2013; Iftikhar, Kline and Youngstedt, 2014; Aiello *et al.*, 2016; Iftikhar *et al.*, 2017). However, this increase in publications can lead to “information overload” and make it more difficult for the end-user to access and process pertinent information that could be of benefit to clinical practice (Pollock *et al.*, 2016. p. 2). An approach adopted to address this issue is the overview of reviews (overviews), which “integrate information from multiple

related systematic reviews to provide a comprehensive synthesis of all SR evidence related to a specific clinical question” in one user-friendly document (Pollock *et al.*, 2016. p. 2).

To date, no such overview of reviews has been undertaken with regards to the effects of exercise on OSA in adults. An overview was deemed necessary in the earlier stages of this thesis to a) identify and solidify the most recent key findings/research needs within the field and b) examine the consistency and robustness of the reviews that have been conducted to date.

3.1.1 Aim

The aim of this chapter was to provide an overview of the latest systematic reviews and meta-analyses examining the effects of exercise on OSA in adults.

3.1.2 Objectives of this Chapter

1. To provide a critical analysis of the published evidence syntheses on exercise as a treatment for the symptoms of OSA
2. Examine the consistency across, and quality of, the latest systematic reviews and meta-analyses regarding the effects of exercise on OSA

3.2 Methods

This overview of reviews was registered with PROSPERO (CRD42013006052) (Appendix three). Searches were conducted in August 2016 and updated in November 2017. The databases Scopus, CINAHL, Ovid, Web of Science and the Cochrane Library (Cochrane Reviews) were searched from 1980 to November 2017. The search was refined to look only in the search field ‘title’ in each database. It was thought that because the key search terms were such important descriptors of the work, they would be in the ‘title’ of all relevant articles. The search strategy is provided in

appendix four. Search terms were designed to target reviews that met the following specific inclusion criteria:

- Published review papers dedicated to studies on the specific population of adults (males and females ≥ 18 years old) diagnosed with having OSA
- Reviews in which studies on the effects of exercise interventions on OSA were considered (physically active exercise interventions and not e.g. oropharyngeal exercises). Reviews were only included if they stated the words 'exercise/lifestyle intervention' in their title.
- Reviews needed to have specifically included a meta-analysis on the studies in which the effects of exercise on the AHI outcome (measured on a continuous ratio interval measurement scale) pre- and post- intervention were quantified.
- Be classified as a systematic review/meta-analysis (as stated in the title)
- Reviews/meta-analyses of RCTs or non-RCTs were considered.

Reviews/meta-analyses were excluded from this overview if they:

- Predominantly focused on studies looking at the effects of weight loss/diet on OSA
- Were a conference abstract
- Were not written in the English language
- Were reviews on diagnosis issues
- Focused on surgical interventions for OSA

Two researchers (SS, GA) independently screened titles and abstracts for eligible reviews. SS and GA agreed upon and obtained full papers for eligible articles. SS and GA independently assessed the eligible articles and unanimously agreed on the final papers for inclusion in this overview. If had been needed, any disagreements between the two reviewers would have been resolved through discussion/contacting a third reviewer.

Data for each review was extracted manually by one author (SS) and collated in tabular format. Data extracted included the review aim, study inclusion criteria for the review and, in particular, the meta-analysis results for AHI, ESS and BMI. The reviewers (GA, SS) met to discuss and review the data that had been extracted by SS. A valid and reliable tool, the AMSTAR (Appendix five), was used to assess the methodological quality of each review (Shea *et al.*, 2007; Shea *et al.*, 2009). The AMSTAR consists of 11 criterion items, with each awarded a score of one if the specific criterion is met for that item (item answer = 'yes') and a score of zero if the criterion is not met (item answer = 'no', 'not applicable' or 'can't answer') (Sharif *et al.*, 2013). An overall AMSTAR score was calculated for each paper and categorised as high (8-11), medium (4-7) or low (0-3) (Sharif *et al.*, 2013). Two researchers (SS, GA) agreed on the AMSTAR score for each review.

No statistical analyses or additional meta-analysis were performed for the present overview of reviews, but verity of individual trial data extraction in each review was scrutinised. A critical analysis of the reviews was presented using a narrative synthesis. All work in this chapter was conducted using expert advice from a current paper by Pollock *et al.*, (2017), 'Selecting and implementing overview methods: implications from five exemplar overviews' and a paper by Smith *et al.*, (2011), 'Methodology in conducting a systematic review of systematic reviews of healthcare interventions'.

3.3 Results

3.3.1 Search Results

A total of 97 references were retrieved from the searches. Of these, 91 were excluded by their title/abstract, as they did not meet the inclusion criteria. Six papers were obtained for further assessment. Two papers were excluded as they focused predominantly on diet-based interventions. Four reviews (including meta-analyses) were included in the final cohort in the present overview of reviews (Figure 3.1).

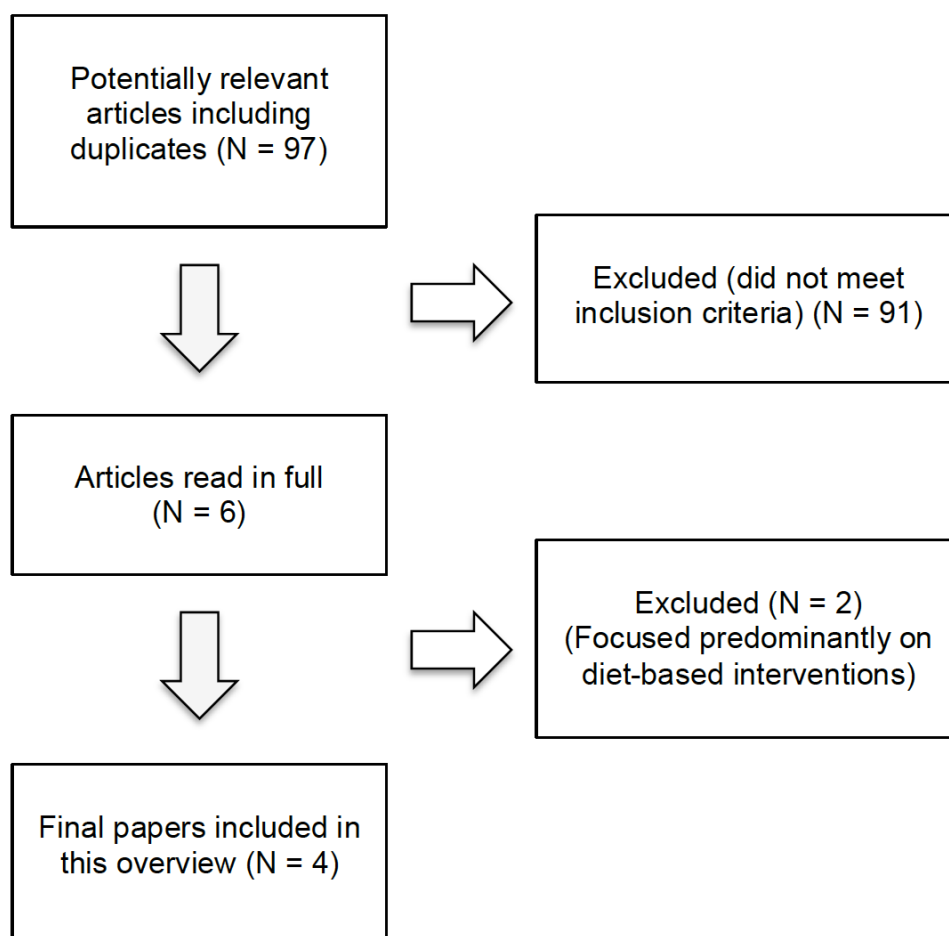


Figure 3.1: Flow diagram for selection of reviews

3.3.2 Characteristics of included reviews

The characteristics of the reviews are detailed in table 3.1. The four reviews and meta-analyses included in this overview were published between 2013 and 2017 (Araghi *et al.*, 2013; Iftikhar, Kline and Youngstedt, 2014; Aiello *et al.*, 2016; Iftikhar *et al.*, 2017). Three reviews were meta-analyses examining both RCTs and non-RCTs (Araghi *et al.*, 2013; Iftikhar, Kline and Youngstedt, 2014; Aiello *et al.*, 2016). The fourth paper conducted a network-meta analysis (NMA) of RCTs (Iftikhar *et al.*, 2017). The NMA technique allows for the comparison of multiple treatments “simultaneously in a single analysis by combining direct and indirect evidence within a network

of randomised controlled trials” (Rouse, Chaimani and Li, 2017. p. 103). This “powerful analytical tool” (Khalifah *et al.*, 2018. p. 1) was employed by Iftikhar *et al.*, (2017) to examine the comparative efficacy of CPAP, MADs, exercise training (studied as a singular intervention) and dietary weight loss for the management of sleep apnoea. In general, the reviews in this overview reported data on studies of healthy males and females who were >40 years old with AHI >15 events/h and BMI >25 kg/m². There was also a trend towards exercise regimens that were aerobic (at least 30 minutes at a moderate intensity), included resistance training and lasted on average 12 weeks (minimum training frequency of three times per week). Each review included no more than eight small exercise studies (number of participants in each exercise study ranged from nine to 25 for non-RCTs and 20 to 45 for RCTs). The minimum number of exercise studies included in a review was four. The AMSTAR scores for the four reviews ranged from 4/11 to 8/11.

Table 3.1: Characteristics of included reviews

Review	Araghi et al., (2013): Effectiveness of lifestyle interventions on OSA: Systematic review and meta-analysis	Iftikhar, Kline and Youngstedt (2014): Effects of exercise training on sleep apnoea: A meta-analysis	Aiello et al., (2016) Effect of exercise training on sleep apnoea: A systematic review and meta-analysis	Iftikhar et al., (2017) Comparative efficacy of CPAP, MADs, exercise-training and dietary weight-loss for sleep apnoea: A network meta-analysis
Primary objective of the review	To conduct a systematic review and meta-analysis to assess the impact of weight loss through diet and physical activity on measures of OSA: apnoea-hypopnoea index (AHI) and oxygen	To evaluate the efficacy of exercise training on OSA severity reduction in adults with OSA	To study the use of exercise (supervised and unsupervised) as management treatment for OSA by analysing the difference in pre and post intervention AHI in adult patients with OSA	To synthesise evidence from available studies to compare the efficacies of supervised aerobic exercise training (studied as a singular intervention), dietary weight loss, MADs, and CPAP in the treatment of sleep apnoea

	desaturation index of 4% (ODI4).				
Search timeframe and databases searched	Main databases searched (Medline from 1948, EMBASE from 1988 and CINAHL from 1982) to 2011 (week 40)	PubMed and Embase from database inception to March 6 th 2013	Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (1993-2014), Web of Science (WOS) and CINAHL	PubMed, SCOPUS, Web of Science and Cochrane Central Register of Controlled Trials from inception to September 8 th 2015	
Types of studies included	1. Studies investigating lifestyle modification interventions (defined as a comprehensive programme of diet and/or exercise therapy without treatment with CPAP at the start of the intervention).	1. Studies reporting exercise as the primary component of an intervention (also reporting changes in cardiorespiratory fitness). 2. Inclusion criteria for RCTs included a diagnosis of OSA and randomisation to	1. Exercise programme duration \geq 2 months 2. Exercise frequency \geq 2 sessions per week 3. Exercise session \geq 30 minutes 4. Exercise as the sole intervention 5. Patient cohort \geq 9 6. Pre and post	1. English language RCTs 2. Only RCTs published in peer-reviewed journals were considered if they studied CPAP, MADs, dietary weight loss, or exercise training (supervised and aerobic) either as an active intervention compared	

	2. Randomised and non-randomised studies that compared a lifestyle modification intervention with no intervention, usual care or placebo. Uncontrolled before-and-after studies were also included.	exercise training or a control condition (stretching exercises or untrained)	intervention changes in AHI, BMI and ESS were reported 7. Randomised trials as well as observational studies were included with no restrictions on language or supervised or unsupervised exercise programme.	with control or as an active comparator with one of the other interventions. 3. Studies had to report either pre-and post-intervention data for outcomes of interest, or data on the difference in outcomes between the intervention and control arms.
Types of studies excluded	Studies using surgical and pharmacological interventions. Studies not in English.	Studies reporting additional intervention with CPAP. Studies reporting data in median and interquartile range	OSA not diagnosed via PSG. Treatment was a combination of exercise and lifestyle intervention. Subjects diagnosed with heart failure, neuromuscular	Surgical weight loss interventions. Studies reporting data in median and interquartile range.

				disorders, COPD. Subjects using dental sleep devices and/or had previously undergone surgery	
Participants	Research papers on male and female adult patients (≥ 18 years old) with a confirmed diagnosis of OSA (AHI ≥ 5 events/h or ODI4 ≥ 5 episodes/h).	Adults with OSA	Adult participants (age > 18 years) with OSA diagnosed via PSG via AHI ≥ 5	Adults with sleep apnoea	
Primary outcomes of interest	OSA severity: AHI Daytime sleepiness: ESS (not reported for exercise-only studies) BMI	OSA severity: AHI Daytime sleepiness: ESS BMI	OSA severity: AHI Daytime sleepiness: ESS BMI	OSA severity: AHI Daytime sleepiness: ESS BMI (reported for exercise training studies only)	

Were study authors contacted?	Authors were contacted to provide additional data where needed.	If the required data from articles were ambiguous or missing study authors were contacted. After two unanswered attempts these studies were excluded from the analysis.	Yes, in the case of missing data authors were contacted for additional unpublished data to complete the dataset	Not reported
External funding	NIHR	The work was supported in part by HL78566 (to SDY) and HL082610 (to CEK)	No	No
Authors declarations	Authors reported no financial conflicts of interest. The work was not industry funded. One author	The authors reported no potential conflicts of interest with any companies or organisations whose	This was not an industry-supported study. The authors have no conflict of interest or financial	IHI, LB, MWD, SDY, UJM report no conflicts of interest. RS, PC and NA detailed any potential conflicts of interest in the

	has received grant support from ResMed, Novo Nordisk, and Lilly.	products or services may be discussed in the article.	involvement with this manuscript.	ICMJE Uniform Disclosure Form for Potential Conflicts of Interest (accessible online via link provided in manuscript)
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Table 3.2: Summary of findings for each review

	Araghi et al., (2013) (Data presented for the exercise-only studies analysed in this paper)	Iftikhar, Kline and Youngstedt (2014)	Aiello et al., (2016)	Iftikhar et al., (2017)
Final studies included in the review	2 RCTs Kline et al., (2011) Sengul et al., (2011) 2 uncontrolled before-after studies Norman et al., (2000) Ueno et al., (2009)	3 RCTs Kline et al., (2011) Sengul et al., (2011) Servantes et al., (2012) 2 single-group intervention studies Barnes et al., (2009)	6 RCTs Guimaraes et al., (2009) Kline et al., (2011) Sengul et al., (2011) Ackel-D'Elia et al., (2012) Schutz et al., (2013) Cavagnoli et al., (2014)	5 RCTs Kline et al., (2011) Sengul et al., (2011) Servantes et al., (2012) (Aerobic-only group) Schutz et al., (2013) Desplan et al., (2014)

		Norman <i>et al.</i> , (2000)	2 single group studies Norman <i>et al.</i> , (2000) Netzer <i>et al.</i> , (2003) (or Giebelhaus <i>et al.</i> , 2000?)	
Exercise interventions in studies reviewed	Predominantly ≤ 6 months aerobic exercise + resistance training			
Participants	<p>Males and females.</p> <p>Predominantly baseline mean:</p> <p>Age > 40 yrs.</p> <p>AHI > 15 events/h</p> <p>BMI > 25kg/m²</p>			

Reported AHI reduction following exercise training (Heterogeneity = I^2)	Mean difference, 95% CI (Inverse variance method, random effects model)	Mean difference, 95% CI (random effects model)	Standardised mean difference? 95% CI (random effects model)	Mean treatment effect, 95% CI (random effects model)
RCT-only analysis	RCT-only analysis -4.66 events/h (-7.87, -1.44) $I^2 = 0\%$	RCT-only analysis -7.17 events/h (-12.48 to -1.87) $I^2 = 0\%$	-0.536 (-0.865 to -0.206) $I^2 = 20\%$	Exercise vs. control
Non-RCT analysis	Non-RCT analysis -10.50 events/h (-16.46, -4.53) $I^2 = 0\%$	RCT + non-RCT analysis -6.27 events/h (-8.54 to -3.99) $I^2 = 0\%$		-17.23 events/h (-25.82 to -8.64)
				P-Score for exercise intervention = 0.63. P-Score ranking places exercise as 2 nd in terms of relative efficacy for AHI reduction.
				1 st CPAP 2 nd Exercise

					3 rd MAD 4 th Weight loss No significant difference between exercise training and the other treatments for AHI reduction
Reported ESS reduction following exercise training (Heterogeneity = I ²)	N/A	Mean difference, 95% CI (random effects model) RCT + non-RCT analysis -3.3 (-5.57 to -1.02) I ² = 82.52%	Standardised mean difference? 95% CI (random effects model) -1.246 (-2.397 to -0.0953) I ² = 86.95%?	Mean treatment effect, 95% CI (random effects model) Exercise vs. control -3.08 (-5.48 to -0.68) P-Score for exercise intervention = 0.75.	

				<p>P-Score ranking places exercise as 1st in terms of relative efficacy for improvement in ESS:</p> <p>1st Exercise 2nd MAD 3rd CPAP 4th Weight loss</p> <p>No significant difference between exercise training and the other treatments in ESS improvement</p>
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Reported BMI reduction following exercise training (Heterogeneity = I ²)	Mean difference, 95% CI (Inverse variance method, random effects model)	Mean difference, 95% CI (random effects model)	Standardised mean difference? 95% CI (random effects model)	Direct pairwise meta-analysis of change in BMI between exercise and controls
	RCT-only analysis	RCT-only analysis		Mean difference, 95% CI (random effects model)
	1.05 kg/m ² (-1.71, 3.81) I ² = 0%	-0.57 kg/m ² (-1.34 to 2.49) I ² = Not reported		-0.61 kg/m ² (-2.31 to 1.10) I ² = not reported
	Non-RCT analysis	RCT + non-RCT analysis		
	-0.49 kg/m ² (-3.20, 2.22) I ² = 0%	-1.37 kg/m ² (-2.81 to 0.07) I ² = 76.92%		

AMSTAR score	8/11	6/11	4/11	8/11
Comments on this review	<p>No publication bias reported</p> <p>Quality assessment of RCTs = Cochrane risk of bias tools (1 exercise RCT low risk of bias across most domains; 1 exercise RCT mixed risk of bias across domains).</p> <p>Quality assessment of non-RCTs = assessment included relevant items from the Effective Practice and Organisation of</p>	<p>No publication bias reported</p> <p>No assessment of individual study quality conducted but a sensitivity analysis was performed. Systematically removing one study at a time demonstrated that no single study changed the statistical significance of the overall results.</p>	<p>No publication bias reported but no plots or test results provided</p> <p>Quality assessment of included studies: Jadad scores between 1 and 4</p> <p>One RCT included breathing exercises alongside exercise program. One RCT included CPAP alongside exercise regimen. One RCT examined oropharyngeal</p>	<p>Analysis selected for assessment of publication bias (ESS analysis) was short of 16 studies included in other analyses and showed apparent bias on visual inspection of the funnel plot</p> <p>Quality assessment of RCTs = modified Cochrane methods. Exercise studies = scored generally low risk of bias for most items except 'blinding of outcomes assessment' item.</p>

	<p>Care Group (EPOC) risk of bias tool for interrupted time-series studies = exercise studies had a number of items in this assessment marked as 'unclear'.</p> <p>Overall quality of studies in this paper described by review authors as poor</p> <p>One RCT included breathing exercises alongside exercise programme. One non-RCT examined heart failure patients. One non-RCT gave</p>	<p>One RCT included breathing exercise programme. One non-RCT provided dietary advice at study entry and unclear whether CPAP used alongside exercise intervention.</p> <p>Some points unclear e.g. whether the SMD or USMD was used as summary statistic in meta-analysis. Reporting errors in paper e.g. inconsistent reporting of heterogeneity for ESS analysis in certain parts of the</p>	<p>exercises. One non-RCT provided dietary advice at study entry and unclear whether CPAP used alongside exercise intervention.</p> <p>Some points unclear e.g. whether the SMD or USMD was used as summary statistic in meta-analysis. Reporting errors in paper e.g. inconsistent reporting of heterogeneity for ESS analysis in certain parts of the</p>	<p>Quality assessment of all studies included in the NMA = risk of bias similar to trend observed in exercise studies.</p> <p>One RCT included breathing exercises alongside exercise programme. One RCT examined heart failure patients.</p> <p>Estimates between 'CPAP: Exercise: MADs' and 'CPAP: Exercise' showed some inconsistency between direct and indirect estimates for</p>
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	<p>dietary advice at study entry and unclear whether CPAP used alongside exercise intervention.</p> <p>In the AHI meta-analysis for this paper the authors presented subgroup analyses for exercise-only, diet-only and exercise/diet combined interventions. They concluded, "Interventions that employed physical activity alone were not successful in reducing AHI</p>		<p>paper, misreporting of information in 'baseline characteristics of studies included in the meta-analysis' table.</p>	analyses on AHI.
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	compared to dietary approaches” and “a combination of diet and physical activity, however, resulted in significant reductions in AHI” (Araghi <i>et al.</i> , 2013. p.1556).			
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3.3.3 Exercise and AHI

All four reviews found that exercise reduced the severity of OSA as assessed using the AHI (Table 3.2). Examining the RCT-only meta-analyses, Araghi *et al.*, (2013) found that exercise-only training in adults with OSA decreased the AHI (mean difference, 95% CI) by -4.66 events/h (-7.87, -1.44, $I^2 = 0\%$) and Iftikhar, Kline and Youngstedt (2014) by -7.17 events/h (-12.48 to -1.87 $I^2 = 0\%$). Iftikhar *et al.*, (2017) also reported a significant reduction in the AHI (mean treatment effect, 95% CI) of -17.23 events/h (-25.82 to -8.64) following exercise training in their NMA. In meta-analyses including non-RCTs, the reduction in AHI following training was (mean difference, 95% CI) -10.5 events/h (-16.46, -4.53 $I^2 = 0\%$) (Araghi *et al.*, 2013) and -6.27 events/h (-8.54 to -3.99 $I^2 = 0\%$) (Iftikhar, Kline and Youngstedt, 2014). Comparing exercise to other interventions for OSA, Iftikhar *et al.*, (2017) reported that there was no significant difference between exercise and any of the other interventions, including CPAP for reducing the AHI (difference between CPAP and exercise = -8.04 events/h, 95% CI -17.00 to 0.92). Exercise also ranked as second out of all the treatments examined in terms of relative efficacy for AHI reduction (P-Score = 0.63) (P-scores were used in this NMA to rank the treatments according to their effectiveness).

3.3.4 Exercise and ESS

The effects of exercise on daytime sleepiness (measured using the Epworth Sleepiness Scale, ESS) were reported in three reviews (Table 3.2). Iftikhar, Kline and Youngstedt (2014) reported reductions in the ESS score of -3.3 points (-5.57 to -1.02 $I^2 = 82.52\%$) post exercise training. In their NMA, Iftikhar *et al.*, (2017) also found that exercise significantly reduced ESS scores (mean treatment effect, 95% CI) by -3.08 (95% CI -5.48 to -0.68). These authors reported that this result placed exercise as first when comparing it against all other treatments investigated in terms of relative efficacy for improvement in daytime sleepiness (P-Score = 0.75).

3.3.5 Exercise and BMI

All four papers indicated that there were no significant changes in BMI following exercise training (Table 3.2). In RCT-only meta-analyses, BMI changes (mean difference, 95% CI) after training were reported as 1.05 kg/m² (-1.71, 3.81, I² = 0%) (Araghi *et al.*, 2013), -0.57 kg/m² (-1.34 to 2.49, I² = not reported) (Iftikhar, Kline and Youngstedt, 2014) and -0.61 kg/m² (-2.31 to 1.10, I² = not reported) (Iftikhar *et al.*, 2017). In meta-analyses including non-RCTs, the changes in BMI (mean difference, 95% CI) were -0.49 kg/m² (-3.20, 2.22, I² = 0%) (Araghi *et al.*, 2013) and -1.37 kg/m² (-2.81 to 0.07, I² = 76.92%) (Iftikhar, Kline and Youngstedt, 2014).

Aiello *et al.*'s (2016) review (Table 3.2) was not included in the main text of the results as there is uncertainty regarding whether the standardised mean difference (SMD) or the unstandardised mean difference (USMD) has been used as the summary statistic in their meta-analysis, which makes it difficult to interpret the results. In their paper, Aiello *et al.*, (2016) do report that exercise training reduced the AHI (-0.536, 95% CI -0.865 to -0.206, I² = 20%) and ESS scores (-1.246, 95% CI -2.397 to -0.0953, I² = 86.95%?) without a significant change in BMI (-0.0473, 95% CI -0.375 to 0.280, I² = 0%).

3.4 Discussion

3.4.1 Exercise and AHI

There is a consistent message throughout the papers reviewed suggesting that exercise significantly reduces the AHI. However, the size of effect is highly variable across the reviews, potentially due to the inclusion of different studies within each analysis. AHI reductions increase from -4.66 events/h (-7.87, -1.44) (Araghi *et al.*, 2013) to -17.23 events/h (-25.82 to -8.64) (Iftikhar *et al.*, 2017) in the RCT-only meta-analyses (Table 3.3). The variation in the sizes of AHI reduction makes it difficult to determine how much exercise can improve OSA severity, especially given the uncertainty in the estimates. Nevertheless, there does appear to be a definite increasing trend towards

values that could clinically improve a patient's OSA e.g. a reduction of seven events/h could change a patient's OSA severity classification from moderate (15-30 events/h) to mild (5-14 events/h) and possibly alter clinical management of the disorder (Danjoux and Habgood, 2016).

Table 3.3: Reductions in AHI following exercise training for RCT-only analyses

Review	AHI reduction (events/h)	95% CI
Araghi <i>et al.</i> , (2013)	-4.66 (Mean difference)	-7.87 to -1.44
Iftikhar, Kline and Youngstedt (2014)	-7.17 (Mean difference)	-12.48 to -1.87
Iftikhar <i>et al.</i> , (2017)	-17.23 (Mean treatment effect)	-25.82 to -8.64

In order to treat patients most effectively it is important to understand how interventions for OSA compare against each other. An interesting finding from the NMA was that there was no significant difference between exercise and any of the other treatments for reducing the AHI, including CPAP, to which exercise ranked in second place in terms of relative efficacy for AHI reduction (difference of -8.04 events/h, 95% CI -17.00 to 0.92) (Table 3.2). This particular result is encouraging given that CPAP is the 'gold standard' treatment for OSA (NICE, 2008). However, it must be noted that Iftikhar *et al.*, (2017) found that in the estimates between 'CPAP: Exercise: MADs' and 'CPAP: Exercise' there were some "statistical conflicts in the network model" between direct and indirect estimates for analyses on AHI (Tonin *et al.*, 2017. p. 4). They state that they could not investigate this inconsistency "due to the frequentist methodology" used in the NMA and advise that the findings for these analyses are interpreted with caution (Iftikhar *et al.*, 2017. p. 12). Moreover, there were a relatively small number of participants in the exercise training studies, which as the authors suggest may have contributed to the

absence of statistical significance in the difference between exercise training and the other interventions. These observations indicate that further research is most definitely needed before conclusions can be made regarding how exercise compares to CPAP for reducing OSA severity.

Comparisons of exercise to other interventions were also made in Araghi *et al.*'s (2013) review (Table 3.4). In their meta-analysis, these authors compared the effect of exercise-only, diet-only and exercise/diet combined interventions on the AHI. They concluded, "interventions that employed physical activity alone were not successful in reducing AHI compared to dietary approaches" and "a combination of diet and physical activity, however, resulted in significant reductions in AHI" (Araghi *et al.*, 2013. p.1556). This indicates that exercise-only interventions are not as good as dietary approaches for treating OSA. However, it is felt that the strength of Araghi *et al.*'s (2013) conclusions cannot be completely agreed with for a number of reasons, namely, a) there is overlapping of confidence intervals, indicating that the 'true' effect for the results could actually be similar between the approaches, b) there is high heterogeneity ($I^2 = 92\%$ for RCTs and $I^2 = 94\%$ for non-RCTs) in the diet-only analyses and c) only one study was included in the RCT diet and exercise subgroup meta-analysis (it has been suggested that at least two, and potentially even a minimum of five studies are needed for valid, powerful and transparent analyses in a meta-analysis) (Valentine, Pigott and Rothstein, 2010; Jackson and Turner, 2017). It is therefore not assumed that exercise is inferior to dietary approaches for reducing the AHI, especially as exercise-training studies ranked above dietary-based interventions in Iftikhar *et al.*'s (2017) NMA in terms of relative efficacy for AHI reduction.

Table 3.4: Results from Araghi *et al*'s (2013) meta-analysis examining the effects of diet-only, exercise-only and diet and exercise combined interventions on the AHI (events/h)

RCT analysis	Mean difference (95% CI)	Heterogeneity
Subgroup: Diet	-4.42 (-14.44, 5.61)	$I^2 = 92\%$
Subgroup: Exercise	-4.66 (-7.87, -1.44)	$I^2 = 0\%$
Subgroup: Diet + exercise	-10.00 (-14.36, -5.64)	N/A
Non-RCT analysis		
Subgroup: Diet	-15.00 (-25.56, -4.44)	$I^2 = 94\%$
Subgroup: Exercise	-10.50 (-16.46, -4.53)	$I^2 = 0\%$
Subgroup: Diet + exercise	-7.33 (-13.59, -1.07)	$I^2 = 0\%$

3.4.2 Exercise and ESS

The evidence reviewed suggests that exercise also significantly reduces daytime sleepiness as measured using the ESS. Again, the data are robust, with all three papers examining this outcome finding a significant effect. The sizes of ESS reduction were similar across the reviews, with Iftikhar, Kline and Youngstedt (2014) reporting a reduction in ESS scores (mean difference, 95% CI) of -3.3 (-5.57 to -1.02) and Iftikhar *et al.*, (2017) a reduction (mean treatment effect, 95% CI) of -3.08 (-5.48 to -0.68) (Table 3.2). Iftikhar *et al*'s (2017) NMA also placed exercise as first in terms of it's relative efficacy for ESS improvement when compared to CPAP, MADs and dietary weight loss (P-Score = 0.75). The evidence does strongly suggest that exercise training could be an effective intervention for addressing a highly debilitating effect of the disorder. Nonetheless, further research is needed to build on these preliminary yet promising results, as there are issues that decrease the strength of the data. Firstly, there was high heterogeneity for the ESS outcome in Iftikhar, Kline and Youngstedt's (2014)

meta-analysis ($I^2 = 82.52\%$) and these authors did not present a separate RCT-only analysis for this outcome. Additionally, the results from Aiello *et al.*'s (2016) review, which again support the beneficial effect of exercise training on the ESS, are unclear due to uncertainty regarding their meta-analysis summary statistics.

3.4.3 Exercise, BMI and mechanisms of effect

An interesting finding from this overview is that the improvements in OSA severity were not accompanied by significant changes in BMI. This observation held true across all papers. However, there is high heterogeneity reported for the BMI outcome ($I^2 = 76.92\%$) in Iftikhar, Kline and Youngstedt's (2014) meta-analysis (Table 3.2). On further inspection of their forest plot, it would seem that data from one of the single group intervention studies by Barnes *et al.*, (2009) (which employed a very low calorie diet alongside the exercise intervention and reported a much larger reduction in BMI compared to the other studies presented in the forest plot) may be responsible for this. Therefore the BMI findings are still considered to be robust and provide good evidence to support the proposal that there are 'exercise-specific' mechanisms responsible for the positive effects of exercise on OSA.

The reviews provided a number of these mechanistic explanations, predominantly related to a) site-specific reductions in fat depositions in structures surrounding the upper airway (increasing pharyngeal lumen size), b) changes in muscle tone in the upper airway (potentially helping to maintain airway patency during sleep) and c) decreases in central fat tissue independent of weight loss (abdominal adiposity in particular has a negative effect on respiratory mechanics) (Araghi *et al.*, 2013; Iftikhar, Kline and Youngstedt, 2014; Iftikhar *et al.*, 2017). It was also proposed that exercise might lead to the normalisation of chemoreceptor sensitivity (which could possibly improve breathing) and increase the time spent in slow-wave sleep, a sleep stage associated with enhanced airway stability (Araghi *et al.*, 2013; Iftikhar, kline and Youngstedt, 2014). Perhaps the most researched

mechanism of effect proposed by the reviews pertains to the 'rostral fluid shift' (the movement of fluid accumulated in the lower extremities during the daytime to the rostral area when lying down to sleep at night), which has been implicated in upper airway collapse (see chapter two, section 2.5.1) (Redolfi *et al.*, 2009; Iftikhar, Kline and Youngstedt, 2014). Further in-depth analysis of these intriguing mechanisms is most definitely needed to improve understanding and treatment of the disorder.

3.4.4 Quality of reviews in this overview

The four reviews in this overview had AMSTAR scores of between 4/11 and 8/11, categorising them as medium to high quality given recommendations from the literature (high quality = 8-11, medium quality = 4-7 or low quality = 0-3, Sharif *et al.*, 2013) (Table 3.2). The lowest score was recorded for Aiello *et al.*'s (2016) review. Although the results do support the findings in the other reviews, there are concerns about the overall quality of evidence in this paper. Firstly, it is uncertain as to whether the authors have used the SMD or the unstandardised mean difference (USMD) as the summary statistic in their meta-analysis. In the abstract, methods and written text of the results section, Aiello *et al.*, (2016. p.86) refer to the USMD, e.g. "data was pooled using USMD due to the uniformity of scale and analysis". However, in the actual forest plots and discussion, reference is made to the SMD. It appears very much like the SMD has been used to summarise the data when examining the actual numbers presented for the AHI reduction (-0.536, 95% CI -0.865 to -0.206), yet the results for the ESS outcome could be perceived as either a SMD or an USMD (-1.246, 95% CI -2.397 to -0.0953). Further concerns are raised by the absence of plots/test values from the assessment of publication bias and reporting errors e.g. inconsistent reporting of heterogeneity for ESS analysis in certain parts of the paper and incorrect information provided in 'baseline characteristics of studies included in the meta-analysis' table. These ambiguities and errors decrease confidence in the results of Aiello *et al.*'s (2016) review. The other three reviews were of a higher quality. Nonetheless, duplicate study screening was not conducted following the initial search in Iftikhar *et al.*'s (2017) NMA and they reported

that publication bias assessment (which detected an apparent bias on visual inspection of the funnel plot) was short of 16 studies and thus not representative of all studies analysed. These increased chances for bias need to be considered when reflecting on the results.

3.4.5 Strengths and limitations of this overview

The work in this chapter was conducted in a systematic and comprehensive manner, examining the latest research within the field of exercise and OSA. Moreover, by adopting strict inclusion criteria, this overview of reviews was able to examine, as far as possible, the ‘exercise-specific’ effects of exercise on OSA (excluding papers without an exercise-only meta-analysis for AHI reduction). However, there are limitations to the work that need to be discussed. Firstly, this overview does not examine the longer-term effects of exercise on OSA as all four papers examined studies lasting no more than 24 weeks. There were also a number of quality-related issues across the reviews as discussed in section 3.4.4 that may decrease the strength of the evidence presented (e.g. reporting errors, publication bias). Further, the quality of the primary studies across the reviews was not optimal and two of the studies examined in the reviews included patients with heart failure (Ueno *et al.*, 2009; Servantes *et al.*, 2012), which may reduce the ability to generalise from some of the data. A number of the primary studies also employed additional interventions alongside exercise training (e.g. breathing exercises, CPAP). However, these additional interventions are not felt to have affected the main conclusions, especially as a sensitivity analysis performed in Iftikhar, Kline and Youngstedt’s review (2014) (conducted by systematically removing one study at a time from the analysis) indicated that no one study changed the statistical significance of the overall results. Finally, it is felt that the AMSTAR tool used to examine the methodological quality of the 4 papers most likely did not provide a comprehensive enough of an assessment for the final paper by Iftikhar *et al.*, (2017), who applied a novel NMA approach to the research (Ge *et al.*, 2016). The AMSTAR was also originally developed for use with reviews of RCTs only and in this

overview, three of the reviews included both RCTs and non-RCTs (Pieper *et al.*, 2018).

3.5 Conclusions

This overview provides robust evidence to suggest that in adults with OSA exercise has a significant and potentially clinically meaningful effect on reducing OSA severity and daytime sleepiness, independent of BMI.

3.5.1 Implications for practice

This overview indicates that exercise may be a very valuable treatment option that compares well with current therapies for reducing the AHI. Although the evidence presented does not allow for certainty regarding the effect size, it does indicate that exercise training could be clinically effective. As highlighted in the discussion, a reduction of seven events/h could change a patient's OSA severity classification from moderate (15-30 events/h) to mild (5-14 events/h) and potentially modify clinical management of the disorder (Danjoux and Habgood, 2016). Therefore, it is fair at present to agree with Iftikhar *et al.*'s (2017. p. 12) proposal, which suggests that exercise training should be used as an "adjunctive therapy" option for reducing the AHI until future work identifies the 'true' magnitude of its effect on the disorder.

Current evidence suggests that exercise training also has a beneficial effect on daytime sleepiness. The size of the effect, a reduction in the ESS of three points, is encouraging and may be clinically important as Patel *et al.*, (2018) propose that the minimum clinically important improvement in the ESS lies between minus two and minus three points. Moreover, exercise training could be more effective for treating daytime sleepiness than CPAP (CPAP has been shown to reduce the ESS by less than three points in recent analyses (Bratton *et al.*, 2015; Iftikhar *et al.*, 2017)). Therefore, it is proposed that patients and clinicians consider using exercise, which also has other important health benefits, for improving this outcome. However, it should be

noted that there is still a need for further research to more confidently support this recommendation.

3.5.2 Implications for research

It is evident from the results of this overview that exercise has a role to play in the treatment of OSA. Further research is certainly warranted and it is suggested that researchers conduct high quality RCTs using larger and more diverse sample groups and longer research timeframes to build on this promising evidence base. Researchers should particularly examine pertinent issues such as, a) clarifying how large of an effect exercise has on reducing the severity of OSA, and b) whether exercise is the most effective treatment for addressing daytime sleepiness associated with the disorder.

Chapter Four: The cross-sectional association between walking speed and obstructive sleep apnoea in a multi-ethnic sample of older men and women

4.1 Introduction

Sleep-disordered breathing is not uncommon in middle-to-old-age adults, with current evidence indicating prevalence rates of more than 15% in this population group (Endeshaw *et al.*, 2009; Marti-Soler *et al.*, 2016). Screening for the disorder is of paramount importance from both public health and economic perspectives (Chung *et al.*, 2013). As discussed in chapter two, current screening is limited by costly and time-consuming procedures. Consequently, there is interest in developing alternative diagnostic tools to address these problems.

Although the potential physiological mechanisms have not yet been fully elucidated, there is now a substantial body of research indicating that decreased physical activity is associated with worse severity of SDB (Peppard and Young, 2004; Iftikhar *et al.*, 2017; Kline *et al.*, 2017). The body of work analysed in chapter three is testament to this. Therefore, it is plausible to suggest that physical activity could provide an avenue for improving the screening of OSA. However, no screening tool has, to date, included an item relating to physical activity.

One indicator of physical activity, which is also a robust indicator of general frailty, has been reported to be walking speed (Stanaway *et al.*, 2011). Health-related thresholds for low and high walking speeds have recently been formulated (Cesari *et al.*, 2005). Therefore, it was hypothesised that a simple 'yes/no' question, similar to those in existing screening tools, but pertaining to reported walking speed, is associated with the severity of SDB. In this chapter, this hypothesis was tested with the large population-based dataset from the Multi-Ethnic Study of Atherosclerosis (MESA).

4.2 Methods

4.2.1 The MESA

The MESA is a large population-based study examining the early stages of cardiovascular disease. The research objectives and design have been published elsewhere (Bild *et al.*, 2002). The MESA study was approved by the local Institutional Review Boards of each participatory study site. The local research ethics committee approved this cross-sectional analysis of the MESA dataset. The study also meets the ethical standards of the International Journal of Sports Medicine (Harriss and Atkinson, 2013).

4.2.2 The MESA participants

The MESA participants were 6814 men (47%) and women (53%) aged between 45-84 years from six communities in the United States of America. Participants were from four different ethnic groups; white (39%), African-American (28%), Hispanic (22%) and Chinese-American (12%). Data for the MESA were collected during five examination points over a 12-year period. Data for the present study were analysed from MESA exam two, undertaken between 2002 and 2004.

4.2.3 SDB outcomes in the MESA

The outcomes relating to SDB were physician-diagnosed sleep apnoea, self-reported apnoeic events, loud snoring heard behind a closed door and daytime sleepiness. These outcomes were measured using a self-administered sleep questionnaire, as detailed previously by Yeboah *et al.*, (2011). Participants could choose from a list of answers for each question with 'don't know' provided as a response for apnoea and snoring items. Guidelines from the American College of Physicians indicate that polysomnography has, and continues to be used routinely for the diagnosis of OSA (Qaseem *et al.*, 2014). Therefore, it is reasonable to assume that

participants who answered 'yes' to the question relating to physician-diagnosed sleep apnoea had undergone polysomnography as part of their diagnostic pathway (Ryan *et al.*, 1995).

4.2.4 Walking speed in the MESA

An interviewer-administered physical activity questionnaire was also completed. One question was: '*When you walk outside of your home, what is your usual pace?*' Five response options were provided from 'no walking at all' to 'brisk or striding'. Self-reported walking speed has been shown to be a good marker of measured walking speed in older adults in a recent large population-based study (Syddall *et al.*, 2015). To facilitate a simple 'yes/no' context in keeping with the traditional screening tools, a walking speed <0.89 m/s (or no reported walking) was classified as 'slow', with ≥ 0.89 m/s classified as 'average/ brisk'. The threshold used to define slow walking speed was informed by Stanaway *et al.*, (2011), who reported that walking slower than 0.89 m/s was predictive of mortality.

4.2.5 Additional MESA measurements

The self-reporting of the relevant variables in the MESA is in the tradition of items on the current clinical STOP-Bang screening tool and facilitates a large sample of participants for data analysis. The other study covariates included age, sex and ethnicity. Each participant's BMI and blood pressure were measured during clinical evaluation (Bild *et al.*, 2002).

4.2.6 Data reduction

All outcome variables were dichotomised in keeping with current screening tools, such as the STOP-Bang. Responses to the '*how loud is your snoring?*' question in MESA were recoded into whether snoring was 'extremely loud-can be heard through a closed door' or not. Responses to '*how often do you feel excessively (overtly) sleepy during the day?*' were recoded into

'never/sometimes' and 'often/almost always'. Other items, including physician-diagnosed sleep apnoea were already in a dichotomised format.

4.2.7 Data analysis

Data analysis was completed in the Statistical Package for the Social Sciences (SPSS, version 21) and Stata (StatCorp, Texas, version 12.1). Data were analysed with multivariable-adjusted binomial regression (with an identity link function), providing risk differences and their confidence intervals (95% CI). Analyses were adjusted for age, sex and ethnicity. Multivariable-adjusted Cox regression with a constant time-to-event variable (Barros and Hirakata, 2003) was employed to derive prevalence risk ratios and associated 95% CIs for the six STOP-Bang items, as well as for the additional slow-walking speed question. The minimum clinically important effect was defined as a prevalence risk ratio of 1.11. This effect size implies that for every 10 people with sleep apnoea who have a slow walking speed there are nine people with sleep apnoea who have a fast walking speed; that is, one in 10 sleep apnoea cases is associated with a slow walking speed. Thresholds for moderate, large, very large and extremely large effects were deemed to be risk ratios of 1.43 (10/7), 2 (10/5), 3.3 (10/3) and 10 (10/1), respectively.

4.3 Results

Faster walkers were, on average, 3.5 years younger and 2.3 kg/m² lower in BMI than slower walkers. Faster walkers also comprised a lower proportion of women and African-American participants and a higher proportion of white participants (Table 4.1). The mean total number of medications was slightly (0.4) higher in slow walkers than in average/brisk walkers.

Table 4.1: Characteristics of the slow and average/brisk walkers at examination two in the MESA sample

Characteristic	Slow Walkers (N=1649)	Average/brisk walkers (N=4476)	95% CI for difference
Age (mean ± SD years)	66.2 ± 10.2	62.7 ± 9.9	2.9 to 4.1
BMI (mean ± SD kg/m²)	30.0 ± 6.2	27.7 ± 5.0	2.0 to 2.6
Proportion women (%)	59%	50%	6% to 12%
Total no. of medications (mean ± SD)	5.4 ± 3.8	5.0 ± 3.7	0.2 to 0.6
Ethnicity proportions (%)			
White	31%	43%	-9% to -15%
African-American	38%	23%	12% to 18%
Hispanic	22%	21%	-1% to 3%
Chinese-American	9%	13%	-2% to -6%

* SD = standard deviation; CI = confidence interval

The prevalence of SDB outcomes in the dataset is presented in table 4.2. The prevalence of physician diagnosed sleep apnoea, self-reported apnoeas

and loud snoring was higher in men compared with women (4.8 vs. 2.3 %, 11.0 vs. 5.9 % and 23.6 vs. 16.9% respectively).

Table 4.2: The prevalence of SDB outcomes in men, women and the overall MESA sample

SDB outcome	Prevalence in Men	Prevalence in women	Overall prevalence N (%)
Physician-diagnosed sleep apnoea	140 / 2912 (4.8%)	73 / 3213 (2.3%)	213 / 6125 (3.5%)
Self-reported apnoeas	240 / 2168 (11.0%)	138 / 2335 (5.9%)	378 / 4503 (8.4%)
Loud snoring	347 / 1472 (23.6%)	204 / 1207 (16.9%)	551 / 2679 (20.5%)
Daytime sleepiness	637 / 2950 (21.6%)	740 / 3245 (22.8%)	1377 / 6195 (22.2%)

*The denominators vary for different outcomes depending on the number of 'don't know' responses to each STOP-Bang question

Slower walking speed was associated with an increased risk of all outcomes indicative of SDB, including physician-diagnosed sleep apnoea (Table 4.3). These risk differences were adjusted for sex, age, and ethnic group. No substantial interactions were found between walking speed, ethnic group and sex. Risk differences were also similar when people who reported no walking at all were removed from the analyses.

Table 4.3: Multivariable-adjusted risk differences between slow and average/brisk walkers for SDB. Multivariable risk differences were similar across ethnic groups; for men and women; when people who reported no walking at all were removed from the analysis.

Study outcome	Risk ('slow' walking speed)	Risk ('average/brisk' walking speed)	Risk difference	95% CI
Diagnosed sleep apnoea	4.7%	3.2%	1.5%	0.4% to 2.5%
Self-reported apnoeic events	10.7%	8.7%	2.0%	0.1% to 3.8%
Loud snoring	24.9%	20.1%	4.8%	1.2% to 8.3%
Daytime sleepiness	26.4%	21.0%	5.4%	3.0% to 7.8%

* CI = confidence interval

In this chapter, it was also investigated whether slow-walking speed was an independent risk factor for physician-diagnosed sleep apnoea compared with other 'yes/no' type outcomes present in traditional OSA screening tools. Questions relating to apnoea incidence and loud snoring were, as expected, the strongest independent predictors of sleep apnoea (Table 4.4). Body mass index was also an independent predictor of sleep apnoea (prevalence risk ratio: 1.7). Nevertheless, the strength of the independent association of slow-walking speed was approaching that of BMI. People who walked relatively slowly had 1.5-times the risk of having sleep apnoea compared with people who walked at a faster pace. This prevalence risk ratio was higher than the point estimates of the prevalence risk ratios for the screening items of daytime sleepiness, sex and hypertension (Table 4.4).

Table 4.4: Multivariable-adjusted prevalence risk ratios for the slow-walking speed question and other ‘yes/no’ questions traditionally included on screening tools such as the STOP-Bang tool.

STOP-Bang variable	Prevalence risk ratio	95% CI	
Stopping breathing during sleep	21.9	12.6	38.0
Loud snoring	2.1	1.5	3.1
BMI	1.7	1.2	2.5
Slow walking speed	1.5	1.0	2.1
Daytime sleepiness	1.3	1.0	1.8
Sex	1.3	0.8	1.9
High blood pressure	1.2	0.9	1.7

*CI = confidence interval

4.4 Discussion

In this chapter, the hypothesis that a simple ‘yes/no’ walking speed question is associated with the severity of outcomes related to SDB was tested using the MESA dataset. Slow-walking speed was independently associated with an increased risk of SDB outcomes in this large population-based work. Moreover, the simple walking speed question compared favourably with other items present on existing screening tools for SDB, including sex, daytime sleepiness and hypertension.

The prevalence of diagnosed sleep apnoea was greater in men (4.8%) than in women (2.3%). Nevertheless, the multivariable-adjusted association between sex and sleep apnoea was weak and not statistically significant (Table 4.4), suggesting that other covariates, such as BMI, might be more influential than sex *per se*. In this chapter, a substantial interaction between

sex and slow-walking speed – sleep apnoea association was not found. Endeshaw *et al.*, (2009) analysed a population-level dataset (The Cardiovascular Health Study) and reported an association between slow-walking speed and SDB, but only in women. The authors reported that this sex-specific finding was unexpected, but postulated that the protective effect of female hormones on airway collapse is lost after the menopause.

Endeshaw *et al.*, (2009) obtained polysomnographic data from their participants while they slept at home, allowing the quantification of the rate of apnoeas and hypopnoeas, in contrast to the self-report approach employed in the present study. Nevertheless, the sample size in the current study was substantially larger than theirs (N = 6125 vs. 1042), providing greater precision of estimation of effects in both sexes. In agreement with the present findings, data from the Wisconsin Sleep Cohort Study indicated that the association between habitual exercise and SDB was similar between men and women (Peppard and Young, 2004). Further large population-based research employing direct polysomnography, the ‘gold standard’ diagnostic test for OSA, is needed to clarify any sex differences in risk factors for SDB (Chung *et al.*, 2013).

The prevalence of the SDB outcomes in the sample analysed, including sleep apnoea, is consistent with those reported in other large studies (Young *et al.*, 1993; Enright *et al.*, 1996; Pallesen *et al.*, 2007). Sleep apnoea can present itself as obstructive, central or mixed (obstructive/central) in nature. Although the word ‘obstructive’ was not included in the sleep history questionnaire in the MESA, the prevalence of central and mixed sleep apnoea is much rarer in the general population than is OSA (White and Bradley, 2013). Therefore, it is likely that the vast majority of cases of diagnosed sleep apnoea in the present study are obstructive in nature. The present study findings support the hypothesis that low levels of physical activity increase the severity of SDB. One possible causal pathway for this hypothesis involves a bidirectional influence of obesity (Figure 4.1). A habitual slow walking pace may, over time, contribute to weight gain, which is an independent risk factor for SDB (Riad and Chung, 2013). Conversely, it

is possible that more severe SDB mediates more daytime sleepiness and, therefore, a decreased willingness or propensity for physical activity and a faster walking pace (Chennaoui *et al.*, 2015). This pathway is supported by population-based research, which has found a statistically significant association between sleepiness and a decreased walking speed (Stenholm *et al.*, 2010). Because BMI is on this potential causal pathway, it was not adjusted for in the primary analysis of risk differences.

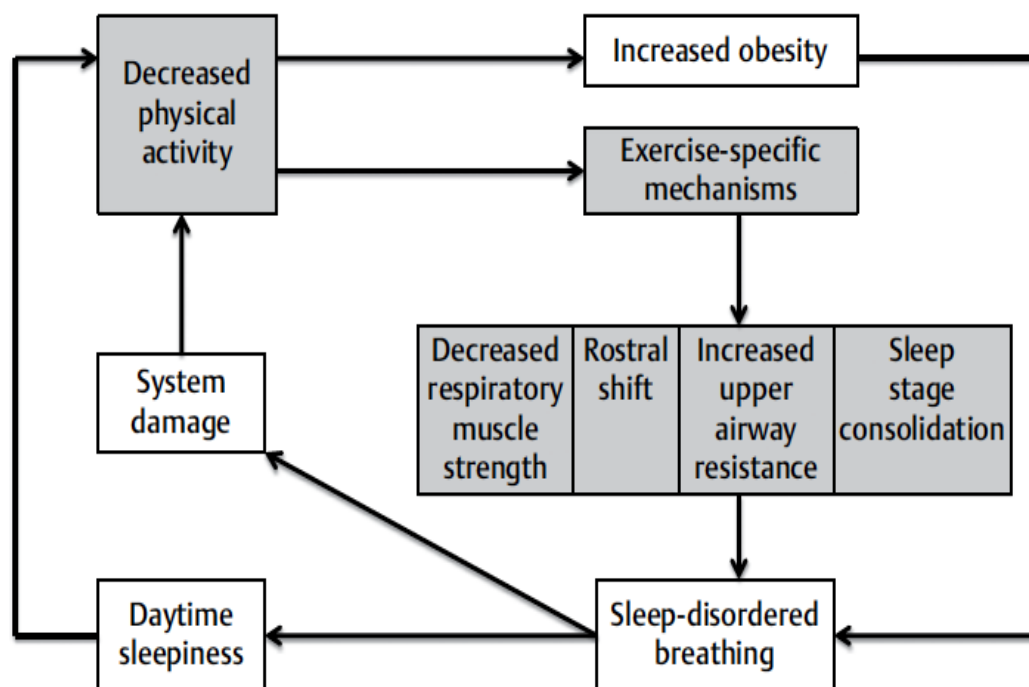


Figure 4.1: The potential causal pathway(s) between physical activity and severity of sleep-disordered breathing (Suri *et al.*, 2015).

Nevertheless, in a follow-up analysis, slow-walking pace was compared against other items, including BMI, on popular screening tools for SDB. Slow-walking pace was found to be independently associated with the prevalence of self-reported diagnosed sleep apnoea, with a point estimate prevalence risk ratio that was slightly larger than those relating to sex, daytime

sleepiness and hypertension. This finding was consistent even if the participants who reported no walking at all were removed from the analysis. In terms of clinical relevance, the point estimate for the prevalence risk ratio for walking speed represents a moderate effect size, but the uncertainty (quantified by the 95% CI) is such that the true population effect could be trivial (< 1.11) to large (>2).

It is plausible that the causal pathway between walking speed and SDB involves 'exercise-specific' mechanisms, independent of BMI (Figure 4.1) (Peppard and Young, 2004; Iftikhar, Kline and Youngstedt, 2014). As previously explained in chapters two and three, a number of mechanisms mediating these changes have been postulated in the literature. At present, it is believed that being physically active may decrease OSA severity by increasing upper airway dilator muscle strength, reducing nasal resistance, improving sleep architecture and preventing lower-extremity fluid accumulation (via the skeletal-muscle pump, the 'Rostral Fluid Shift' hypothesis) (Kline *et al.*, 2011; Mirrakhimov, 2013; Kline *et al.*, 2017). All of these exercise-mediated changes may help to maintain airway patency during sleep and thus improve SDB (Kline *et al.*, 2011). However, there is still a paucity of data to allow for any firm conclusions to be made regarding the specifics of any of these potential mediating mechanisms, exercise and OSA.

In the MESA, only 4205 people answered the question relating to loudness of snoring, with 1526 participants reporting 'don't know'. The response rate for self-reported perceptions of apnoea during sleep was also poor (Table 4.2). In contrast, 6125 (98%) of the 6232 participants assessed at exam two were able to answer the walking speed question. Therefore, not only might the association between walking speed and sleep apnoea be stronger than other proposed risk factors, the question may be more easily-answered by participants than other risk factors.

The large sample in the current study, together with the fact that statistically significant associations were present, indicates acceptable statistical power.

Nevertheless, a limitation is that this work was observational and cross-sectional in nature, with risk of temporal bias. Therefore, one can only speculate, as has been done above, about proposed causal mechanisms. However, the finding that walking speed (an indicator of physical activity and general frailty) is associated with less severe SDB, independent from BMI, agrees with the evolving body of research, including a recent network meta-analysis (NMA) of RCTs examining the effects of supervised exercise interventions on sleep apnoea (chapter three) (Karlsen *et al.*, 2017; Iftikhar *et al.*, 2017).

4.5 Conclusion

This chapter has reported an independent association between self-reported slow-walking speed and SDB outcomes in a large population-based study. Prospective observational and experimental studies should follow to confirm these encouraging findings. It is therefore proposed that a simple ‘yes/no’ question relating to slow-walking speed could improve the screening utility of the STOP-Bang questionnaire.

The results from the work conducted in this chapter were:

- Presented at the 19th Annual Congress of the European College of Sport Science in Amsterdam, July 2014: Conference abstract ID: 265 (Oral presentation - selected to present in the Young Investigators Award category).

Suri, S., Batterham, A.M., Ells, L., Danjoux, G. and Atkinson, G.

Association between self-reported walking pace and indicators of sleep-disordered breathing: A population-based investigation.

- Written up and published in the International Journal of Sports Medicine (Appendix six).

Suri, S.V., Batterham, A.M., Ells, L., Danjoux, G. and Atkinson, G. (2015)

‘Cross-sectional association between walking pace and sleep-disordered breathing’, *International Journal of Sports Medicine*, 36(10), pp. 843-847.

Chapter Five: Is flow-mediated dilation a useful indicator of cardiovascular risk in patients with obstructive sleep apnoea?

5.1 Introduction

OSA places great strain on the vascular system. Studies, including the large population-based MESA, support a relationship between sleep apnoea and an increased risk of cardiovascular events (Yeboah *et al.*, 2011; Xie *et al.*, 2017). As discussed in chapter two, the causal pathway between sleep apnoea and cardiovascular disease has been proposed to involve the intermediary variables of elevated sympathetic activity, insulin resistance and obesity (Cutler *et al.*, 2002; Jean-Louis *et al.*, 2008). Other abnormalities in coagulation factors, platelet activation, inflammatory processes and/or endothelial function may also play a role in the pathogenesis of cardiovascular disease in sleep apnoea (Jean-Louis *et al.*, 2008; Somers *et al.*, 2008).

The capacity of blood vessels to respond to physical and chemical stimuli in the lumen is imperative to their functional role (Corretti *et al.*, 2002). Ali *et al.*, (2014) recently reviewed the utility of various early indicators of cardiovascular events in OSA. One of these indicators was the percentage of flow-mediated dilation (FMD%), a non-invasive measure indicative of endothelial function in humans (Celermajer *et al.*, 1992). Ali *et al.*, (2014) reported that, in most studies, mean FMD% is lower for patients with OSA vs. healthy participants; an observation corroborated by Hoyos *et al.*, (2015) in a recent review specifically on sleep apnoea and endothelial dysfunction.

The FMD% ratio index is calculated by dividing the change (in response to a stimulus) in arterial diameter by the initial baseline diameter of the artery and multiplying by 100 (Atkinson and Batterham, 2013a, 2013b). In order for FMD% to be a valid indicator of endothelial function (distinct from structure), it is desirable that this ratio index scales consistently over the full range of

measurements. Nevertheless, from the earliest studies onwards, FMD% has been reported to be negatively correlated, sometimes strongly, to initial artery diameter (Celermajer *et al.*, 1992; Atkinson and Batterham, 2013a). Despite some attempts to explain this observation physiologically, there is evidence to suggest that it is due to the poor size-scaling characteristics of the FMD% ratio index itself (Atkinson and Batterham, 2015). This confounding of FMD% is important because initial artery diameter has been reported to predict the progression of subclinical atherosclerosis (Halcox *et al.*, 2009) and cardiovascular events (Yeboah *et al.*, 2009), as well as being substantially higher in OSA patients (Namtvedt *et al.*, 2013).

This potential obfuscation of arterial structure and function by the FMD% index is seldom considered in the relevant literature. For example, less than half of the thirteen studies on FMD% reviewed by Ali *et al.* (2014) actually presented data for initial diameter. In only one of these studies (Namtvedt *et al.*, 2013) was there an attempt to adjust FMD% for initial diameter. Consequently, it has been questioned to what extent the reported lower FMD% in OSA is explained by the potentially higher initial artery diameter in these patients (Atkinson, 2013).

Due to the observed lower FMD% highlighted in patients with OSA (Ali *et al.*, 2014), it is possible that this marker of endothelial functioning may have clinical utility e.g. improve the diagnosis of OSA. The FMD% ratio index could also be used as an outcome measure in future RCTs of the benefits of exercise on OSA (including in the protocol proposed at the end of this thesis). However, before moving forward with FMD%, it is important to address the potential inconsistent size-scaling of this ratio index as it could lead to biased inferences in subsequent work (Lolli, Batterham and Atkinson, 2017).

Therefore, this chapter aimed to quantify any differences in initial brachial artery diameter and flow-mediated dilation (adjusted for initial artery diameter) between people who did and did not report physician-diagnosed

sleep apnoea in the dataset from the Multi-Ethnic Study of Atherosclerosis (MESA). As discussed in chapter four, this dataset has also recently been analysed to explore other questions related to sleep apnoea, predominantly because the dataset is very large, population-based and involved comprehensive and standardised data collection methods (Yeboah *et al.*, 2011; Lin *et al.*, 2015; Chew *et al.*, 2016).

5.2 Methods

5.2.1 The MESA participants

As stated in chapter four, the MESA is a prospective cohort study on subclinical cardiovascular disease. The overall MESA sample comprises 6814 women and men, aged 45–84 years, recruited from six regions in the United States of America. The full study design for the MESA has been detailed by Bild *et al.*, (2002). The MESA was approved by the local Institutional Review Boards of each participatory study site. The local research ethics committee approved this cross-sectional analysis of the MESA dataset.

5.2.2 The sleep apnoea question in the MESA

During the second MESA examination, a self-administered sleep history questionnaire was administered (Yeboah *et al.*, 2011; Lin *et al.*, 2015; Chew *et al.*, 2016). A question was '*Have you ever been told by a doctor that you had sleep apnoea (a condition in which breathing stops briefly during sleep)?*' Participants responses were either 'yes', 'no' or 'don't know'. Among the 6814 MESA participants, 678 either did not participate in the sleep history study or reported 'don't know' to the sleep apnoea question and were therefore excluded from analysis.

5.2.3 The FMD% protocol in the MESA

Full details of the FMD% protocol in the MESA are described by Yeboah *et al.*, (2009) and additional information regarding the scanning and reading protocol is available at the MESA website (www.mesa-nhlbi.org). In brief, brachial FMD% was measured non-invasively using ultrasound with participants in a supine position after 15 minutes rest and a minimum of 6 hours fasting (Yeboah *et al.*, 2009). Images of the right brachial artery (artery imaged 5-9 cm above the antecubital fossa) were obtained using linear-array multifrequency transducer technology operating at 9 MHz (GE Logiq 700 Device) (Yeboah *et al.*, 2009). A standard blood pressure cuff was positioned around the right arm (2 inches below the antecubital fossa) (Yeboah *et al.*, 2009). Once baseline images had been recorded, the cuff was inflated to 50 mm Hg above the participant's systolic blood pressure for 5 minutes (Yeboah *et al.*, 2009). Digitised images of the right brachial artery were captured continuously for 30 seconds before cuff inflation and for 2 minutes beginning immediately before cuff deflation to document the vasodilator response, which is principally mediated by endothelium-derived nitric oxide (Corretti *et al.*, 2002; Yeboah *et al.*, 2009). Of the 6136 participants who recorded a 'yes/no' answer for the sleep apnoea question, 3354 completed the FMD% protocol (1692 women and 1662 men). Of these participants, 104 (23 women and 81 men) reported that a physician had diagnosed them with sleep apnoea, giving an overall prevalence of 3.1% (1.4% in women and 4.9% in men).

5.2.4 Data analysis

Data were analysed using FMD%, and an allometric approach (Atkinson and Batterham, 2013a, 2013b; Atkinson *et al.*, 2013). In this approach, initial and peak diameters are logarithmically transformed (natural logarithm) and the differences between these values are calculated. These differences in diameter on the log scale are entered as the outcome in a general linear model with sleep apnoea diagnosis as the fixed factor and logarithmically-transformed initial diameter as a covariate. The resulting adjusted estimates

of the flow-mediated response and associated 95% confidence intervals are obtained after back-transformation. The allometric scaling exponent of 'b' is derived from the log-linear transformation of the simple allometric model based on the equation;

$$\text{Peak diameter} = a \times \text{initial diameter}^b$$

The FMD% and allometric approaches were compared using unadjusted models and models adjusted for sex, race and age. It is extremely important not to covariate-adjust statistical models for variables that are on the causal pathway between exposure and outcome (Schisterman, Cole and Platt, 2009). This issue has been highlighted by Levitzky and Redline (2009) specifically in the context of OSA and cardiovascular disease. These authors thought it crucial not to adjust for variables such as body mass, diabetes and hypertension when the association between OSA and cardiovascular outcomes is being investigated because these variables are on the proposed causal pathway (Jean-Louis *et al.*, 2008). Therefore, these variables were not entered as covariates in the statistical models used in this chapter.

Any ratio index like FMD% is naturally positively skewed even if the numerator and denominator are normally distributed (Atkinson and Batterham, 2013b). Therefore, the FMD% index was also examined following natural logarithmic transformation. Descriptive sample statistics are mean \pm standard deviation (SD). The precision of inferential estimates is described by the 95% confidence limits.

5.3 Results

The correlation between FMD% and initial diameter was -0.43 (-0.57 to -0.26, $P < 0.0005$) in the sleep apnoea patients (Figure 5.1) and -0.42 (-0.45 to -0.39, $P < 0.0005$) in the undiagnosed participants. When FMD% was log-transformed, these correlations reduced slightly to -0.36 (-0.52 to -0.18, $P < 0.0005$) and -0.40 (-0.43 to -0.37, $P = 0.0005$) respectively. The regression slope for the FMD%-initial diameter relationship was -1.2 %/mm (95%CI: -0.7

to -1.7, $P < 0.0005$) for sleep apnoea patients and -1.5 %/mm (95%CI: -1.4 to -1.6, $P < 0.0005$) for undiagnosed participants.

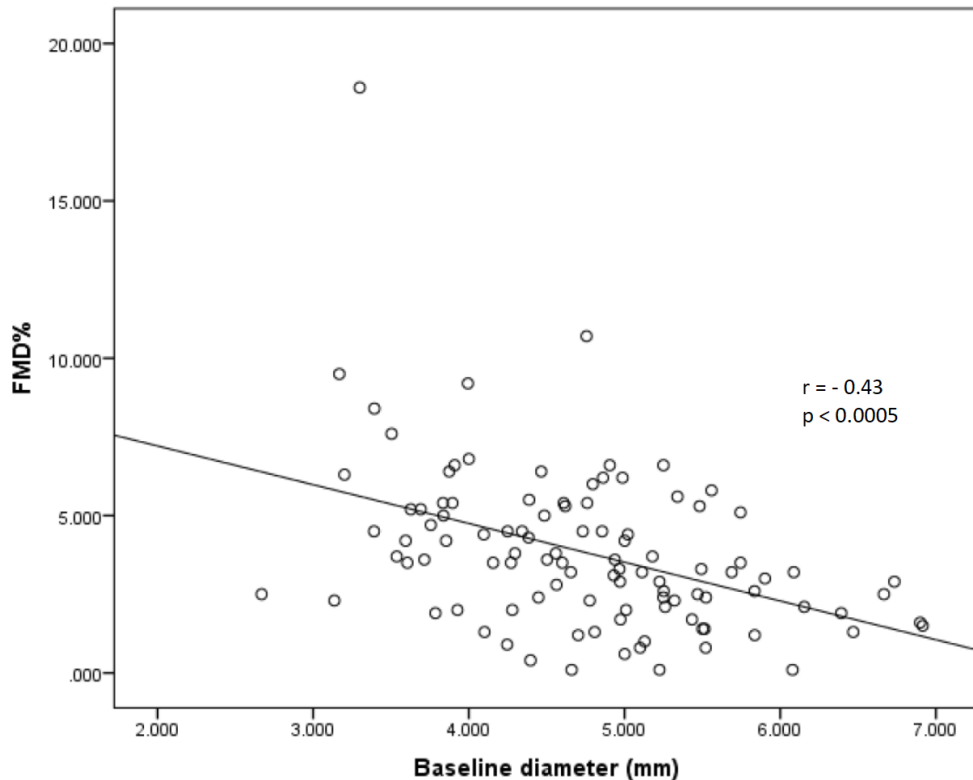


Figure 5.1 The negative moderate correlation between initial artery diameter and FMD% for the sleep apnoea patients in the MESA (Atkinson *et al.*, 2016). This figure shows that FMD% does not scale consistently over the full range of measurements.

The value of 'b' in the allometric model was 0.946 (0.924 to 0.969, $P < 0.0005$) in the sleep apnoea patients and 0.942 (0.937 to 0.946, $P < 0.0005$) in the undiagnosed cohort. A percentage index is accurate for scaling a change in size across the full measurement range only when 'b' = 1.000 (Atkinson *et al.*, 2013).

In the unadjusted model, the sample mean \pm SD estimate of FMD% was $3.8 \pm 2.6\%$ for sleep apnoea patients vs. $4.4 \pm 2.9\%$ for undiagnosed participants (95%CI for difference: 0.01 to 1.14%, $P = 0.045$, table 5.1). In the model adjusted for sex, ethnicity and age, mean \pm SD estimates of FMD%

remained unchanged (3.8 ± 2.7 vs. $4.4 \pm 2.7\%$) and the estimate of the difference between samples became more precise (95%CI: 0.07 to 1.12%, $P=0.028$).

Table 5.1 Variables measured during the flow-mediated dilation protocol for people in MESA who did, and did not, have physician-diagnosed sleep apnoea (estimates not adjusted for race, sex and age).

Variable	Sleep apnoea (N=104) Mean \pm SD	Undiagnosed (N=3250) Mean \pmSD	95%CI for difference between samples
Initial diameter (mm)	4.76 \pm 0.89	4.31 \pm 0.83	0.28 to 0.61
Peak diameter (mm)	4.93 \pm 0.88	4.49 \pm 0.82	0.28 to 0.60
Absolute diameter change (mm)	0.17 \pm 0.10	0.18 \pm 0.11	-0.01 to 0.01
FMD% (%)	3.8 \pm 2.6	4.4 \pm 2.9	0.01 to 1.14
D_{base}-adjusted FMD (%)	4.4 \pm 2.4	4.3 \pm 2.4	-0.5 to 0.5

In the unadjusted model, mean initial diameter was 0.45 mm larger in the sleep apnoea patients (95%CI: 0.28 to 0.61 mm, $P<0.0005$). This mean difference was 0.19 mm (95%CI: 0.07 to 0.32, $P=0.003$) in the model adjusted for sex, age and race. Use of the allometric approach to account for the confounding of initial diameter generally reduced the mean difference in flow-mediated response between sleep apnoea patients and healthy people. In the model adjusted only for initial artery diameter, the sample difference in adjusted flow-mediated dilation was 0.02% (-0.49 to 0.50, $P=0.92$). In the adjusted model, the difference between samples was 0.3% (95%CI: -0.1 to 0.7, $P=0.19$), which is approximately half the mean difference quantified with the FMD% index.

5.4 Discussion

In this chapter, the potential inconsistent size-scaling of the FMD% ratio index was examined in order to appraise its value for further use within the thesis. As previously discussed, it is vital that a ratio index scales consistently over the full range of measurements. In agreement with previous studies (Atkinson and Batterham 2013a, 2013b; Atkinson *et al.*, 2013), the moderate-to-strong negative correlation between FMD% and initial diameter indicates that this assumption is also violated for sleep apnoea patients in the MESA (Figure 5.1). The analyses suggest that the inappropriate scaling associated with FMD% leads to an exaggeration of the difference in flow-mediated response between people diagnosed with sleep apnoea and undiagnosed people in the MESA. Nevertheless, and in agreement with data from some previous studies (e.g., Namtvedt *et al.*, 2013), a clear mean difference in resting brachial artery diameter was found between people with and without sleep apnoea in the MESA.

Most of the past researchers on this topic have administered overnight sleep studies to their participants. Consequently, previous studies have tended to be relatively small and homogeneous in terms of participant sample (Jean-Louis *et al.*, 2008). A meta-analysis of the pooled mean difference in FMD% between people with and without sleep apnoea has yet to be undertaken on these past studies. However, Ali *et al.*, (2014) reported that this mean difference in FMD% tends to be 0.3-3.0%. The sample difference in FMD% in the present study of 0.6% lies within this range. A pertinent point is that statistical analyses have been covariate-adjusted for initial diameter in only one of these previous studies (Namtvedt *et al.*, 2013). This research group reported a substantial influence of initial artery diameter on the FMD% index. When the researchers adjusted for this confounding, the influence of a one-unit change in the AHI on FMD% was reported to be -0.09 % (Namtvedt *et al.*, 2013). Therefore, the difference in FMD% (adjusted for initial diameter) between an AHI of zero and twenty events/h can be estimated from this regression slope to be only 1.8%, which agrees with the clinically

unimportant association found in the current analysis of the large population-based MESA dataset.

This finding indicates that FMD% may not be appropriate to take forward in the thesis and in other trials where future cardiovascular risk is the target outcome, as it could lead to biased inferences and waste vital funding and time (Lolli, Batterham and Atkinson, 2017). The evidence from the current analysis of a large, population-based, multi-ethnic study, which involved comprehensive and standardised data collection methods provides strong support for this proposal. Nevertheless, there are limitations to the work, which need to be discussed before a final conclusion can be made.

In terms of potential limitations, first, this study was based on an observational cross-sectional design, which precludes the elucidation of the temporal relationships between variables in the causal pathway. Although it is thought most likely that sleep apnoea leads to endothelial dysfunction (Jean-Louis *et al.*, 2008), the reverse could also be true. Interventions designed to improve the symptoms of sleep apnoea such as CPAP have been reported to improve FMD% in some studies (Hoyos *et al.*, 2015), but none of these previous researchers has, again, covariate-adjusted the CPAP-mediated change in the flow-mediated response for any CPAP-mediated change in initial arterial diameter.

A second limitation is that the diagnosis of sleep apnoea was based on self-reported information, which may be influenced by recall bias. As discussed in chapter four, the MESA recorded whether participants had ever been physician-diagnosed with sleep apnoea. The word 'obstructive' was not included in the question. However, the prevalence of the other apnoeas (central and mixed) is known to be much lower than that of OSA (Morgenthaler *et al.*, 2006). Therefore, it is likely that the vast majority of the sleep apnoea patients in MESA had OSA. It is also likely that polysomnography was used to diagnose sleep apnoea in the MESA participants who reported diagnosis, as guidelines from the American

College of Physicians indicate that polysomnography has, and continues to be used routinely in the clinical pathway for OSA (Qaseem *et al.*, 2014).

5.5 Conclusion

In conclusion, the sex, race and age-adjusted mean FMD% of the MESA participants who reported physician-diagnosed sleep apnoea was 0.6% lower than those participants who did not report such a diagnosis. This mean difference was 0.3% and not statistically significant when the confounding influence of initial artery diameter was allometrically-adjusted for. Therefore, the MESA participants who reported physician-diagnosed sleep apnoea do not demonstrate a clinically important reduction in flow-mediated dilation. The FMD% ratio index is therefore not carried forward for further exploration in the thesis with regards to the treatment efficacy of exercise on OSA.

The results from the work conducted in this chapter were written up and published in the Journal of Hypertension (Appendix seven).

Atkinson, G., Danjoux, G., Ells, L., **Suri, S.** and Batterham, A.M. (2016) 'Brachial artery diameter, but not flow-mediated dilation, is associated with sleep apnoea in the Multiethnic Study of Atherosclerosis', *Journal of Hypertension*, 34 (3), pp. 410-413.

Chapter Six: Are questions about physical activity and walking speed useful for the screening of obstructive sleep apnoea in weight-loss surgery patients?

6.1 Introduction

The UK has one of the fastest growing obesity rates in the developed world (Reed, Pengo and Steier, 2016). Obesity increases the risk of morbidity and mortality and poses a great challenge to the NHS (McIntosh, Hunter and Royce, 2016; Reed, Pengo and Steier, 2016). In 2016, it was reported that 26.2% of adults in England were obese ($\text{BMI} \geq 30 \text{ kg/m}^2$) and 2.9% were 'morbidly' obese ($\text{BMI} \geq 40 \text{ kg/m}^2$) (Parliament, House of Commons (HOC), 2018). Although the projections are uncertain, forecasting indicates that the economic cost of the nation's increasing prevalence of obesity to the health service alone could reach £8.3 billion by 2025 (Parliament, HOC, 2018).

Bariatric surgery refers to a group of procedures (e.g. stomach stapling, gastric bypasses), which are used to facilitate weight loss in people with a BMI above 40 kg/m^2 or a BMI of $35\text{--}40 \text{ kg/m}^2$ with other comorbidities such as heart disease (NHS Digital, 2018). In 2015/16, bariatric surgeries to treat obesity were performed most commonly in the North East of England (Parliament, HOC, 2018). Such major surgery is not without risks, particularly if an individual also has OSA, as this increases the risk of postoperative respiratory problems, intensive care unit (ICU) admission and can prolong the length of hospital stay (Chung *et al.*, 2013; Riad and Chung, 2013; Chung, Abdullah and Liao, 2016).

Obesity is a known risk factor for OSA, with prevalence rates of the disorder reported in excess of 50% in bariatric populations (de Raaff, de Vries and van Wagenveld, 2018). Pre-operative screening for OSA is essential to optimise this groups' perioperative management and enhance patient safety across the surgical pathway. In order to risk stratify patients for more

extensive diagnostic testing, the STOP-Bang questionnaire (chapter two, section 2.3.2; Appendix one) is recommended (Nagappa *et al.*, 2017b). Although the STOP-Bang is a concise and easy-to-use screening tool, there are still concerns about low specificity leading to high false-positive rates, which may ultimately impact negatively on limited NHS resources (Chung *et al.*, 2013; Chung, Abdullah and Liao, 2016). Alternative scoring models and the addition of further questionnaire items are increasingly being researched in order to improve the diagnostic performance of the STOP-Bang tool (Chung *et al.*, 2013; Chung *et al.*, 2014; Nahapetian *et al.*, 2016; Sangkum *et al.*, 2017).

The evolving body of literature supporting an association between physical activity and the severity of OSA may provide a platform for improving the STOP-Bang's diagnostic utility (Iftikhar, Kline and Youngstedt, 2014; Iftikhar *et al.*, 2017). This proposal is supported by the work conducted in chapter four, which examined data from the large population-based MESA. In this chapter, it was observed that a slower walking speed (an indicator of frailty) was associated with a greater prevalence of SDB, independently from other common screening factors (Suri *et al.*, 2015). The point estimate prevalence risk ratio for slow-walking speed was slightly larger than those found for several established STOP-Bang items, including sex, hypertension and daytime sleepiness (Suri *et al.*, 2015). While these observational data are promising, further research is needed to provide stronger evidence to help guide clinical practice. This is especially important for weight-loss surgery candidates because the BMI item of $> 35 \text{ kg/m}^2$ on the STOP-Bang tool is essentially redundant – it is predicted that almost all these patients will answer 'yes' to this question.

Therefore, in this chapter, the aim was to explore whether the addition of one of two simple and easily reported questions relating to physical activity and everyday walking speed could improve the diagnostic utility of the STOP-Bang tool in weight-loss surgery candidates.

6.2 Methods

This component of the thesis was conducted as part of a service evaluation at James Cook University Hospital (JCUH), Middlesbrough, in collaboration with Teesside University. The Research and Development team within South Tees Hospitals NHS Foundation Trust (STHNHSFT) and the School of Health and Social Care Research Governance and Ethics Committee at Teesside University approved the evaluation (Appendices eight and nine). All data was collected between February 2015 and June 2016.

Patients who meet strict criteria can be referred by their general practitioner into the Bariatric and Specialist Weight Management Services (SWMS) at JCUH for weight-loss surgery (patients must have a BMI $> 40 \text{ kg/m}^2$ or a BMI of $> 35 \text{ kg/m}^2$ with other medical comorbidities, have tried but failed to lose weight through other methods, have weight issues that affect quality of life and health and be fully committed to working with the Bariatric and SWMS team). The Bariatric and SWMS team, which includes dietitians and psychologists, provides comprehensive and multidisciplinary support to all patients in this pathway, e.g. educational support about topics such as preoperative lifestyle changes and information about post surgery and follow up appointments (NHS, 2019).

As part of the normal clinical pathway, all patients referred to bariatric and SWMS clinics at JCUH completed the STOP-Bang screening tool located on the referral form during their first clinical evaluation with a bariatric nurse specialist (Appendix 10). At JCUH, a modified version of the original STOP-Bang questionnaire is employed whereby scores from a validated questionnaire for assessing daytime sleepiness (Epworth Sleepiness Scale, chapter two, section 2.3.2; Appendix two) replace the original STOP-Bang item 'Tired' (*Do you often feel tired, fatigued, or sleepy during the daytime?*) (Johns, 1991; Johns, 1993). A score of ≥ 12 on this scale is dichotomised into a 'yes' for the STOP-Bang tool.

For the current project, patients were asked to complete two physical activity-related questions, which were added to the referral form. These questions were designed to be in keeping with those already present on the STOP-Bang questionnaire i.e. short, simple and requiring a 'yes' or 'no' response. One question examined the patient's routine physical activity participation and one question asked about the patient's everyday walking speed.

Milton, Bull and Bauman (2011) have reviewed a number of single-item physical activity questions in the literature. However, it is felt that none of these items were suitable for the question regarding the patient's routine physical activity participation in the current project. Firstly, a number of the items reviewed by Milton, Bull and Bauman (2011) did not fit the criteria for the current work of needing a binary 'yes/no' response. It was felt that of the questions that did fit the criteria of needing a 'yes/no' response, the majority of these were too specific and not inclusive enough, e.g. they included details on how long/how often the activity had to be or were too suggestive regarding accepted modes of activity.

The remaining single-item question, *"Do you currently participate in any regular activity or programme, either on your own or in a formal class, designed to improve or maintain your physical fitness?"* was very similar to what was needed for the current project (Milton, Bull and Bauman, 2011. p. 204). However, the wording in this question was deemed unsuitable for the current work because it was thought that the word *"currently"* might not have captured what the person did routinely and the phrase *"in a formal class"* was too restrictive regarding how exercise with others had to be carried out (Milton, Bull and Bauman, 2011. p. 204).

For these reasons, a new question was designed for this project, *'Do you routinely participate in any physical activity or exercise (either on your own or with others) to improve or maintain your physical fitness?'* The second question asked, *'When walking during everyday activities, do you find that you have to walk slower than other people?'* These additional questions were not used in any clinical decision-making processes. The validity and reliability

of these new questions have not been tested, but self-reported walking speed has been shown to be strongly associated with measured walking speed in adults (Syddall *et al.*, 2015). Nonetheless, the validity and reliability of the questions used in the current work would be fully examined before being used in formal clinical practice.

Patients with a STOP-Bang score of ≥ 4 (items scored using 'yes' = 1 and 'no' = 0) or patients with a STOP-Bang score of 3 with ≥ 2 relevant comorbidities (type 2 diabetes, cardiac disease e.g. angina/heart failure, significant respiratory disease, e.g. COPD, significant renal disease – CKD ≥ 4) or a BMI ≥ 50 were triaged to the Sleep Medicine department at JCUH for overnight oximetry testing. A sleep consultant made a likely diagnosis of OSA using the oximetry results. Weight-loss surgery patients whose oximetry results suggested a likely diagnosis of OSA were seen in the sleep clinic at JCUH for further clinical evaluation and treatment. NB: At the sleep clinic, full PSG may be employed to confirm the diagnosis of OSA. However, full PSG (which includes EEG) will only be used if deemed necessary (e.g. if the case is complex/unclear) by the clinical specialist, as it is time and labour intensive (Nagappa *et al.*, 2015). Where possible, the clinical specialist will use the oximetry data with the patient's history and clinical examination to confirm the OSA diagnosis during this appointment. As discussed in chapter two (section 2.3.1), this practice is accepted in current clinical guidelines (NICE, 2008; Danjoux and Habgood, 2016; Kapur *et al.*, 2017).

Data analysis was completed in the Statistical Package for the Social Sciences (SPSS, version 24), Stata (Statcorp, Texas, version 14.2) and MedCalc (Ostend, Belgium, version 18.11). All 122 patients responded 'yes' to the STOP-Bang item 'BMI $> 35 \text{ kg/m}^2$ '. Because there was, therefore, no variance in this variable it was not included in the analyses (the model used in analyses was the STOPANG model, with the abbreviation referring to all of the conventional STOP-Bang items). The patients were allocated to one of two groups based on their clinically judged likely diagnosis of OSA (likely diagnosis OSA 'yes' and likely diagnosis OSA 'no'). Demographic (mean, SD) and prevalence (N, %) data for each STOPANG item, slow-walking

speed and low physical activity levels were then computed separately for each group and differences between the two groups calculated (mean difference, 95% CI or % difference, 95% CI). The differences in means for the demographic data were calculated using an independent samples t-test in SPSS. All prevalence figures were obtained from frequency counts in SPSS. A webpage called <http://statpages.info> was used to calculate the confidence intervals for the % difference in prevalence figures. Area under the receiver operating characteristic curve (AUC, 95% CI) was calculated for the three STOPANG models (STOPANG, STOPANG + slow-walking speed item (referred to as WS in the model) and STOPANG + low physical activity level item (referred to as PA in the model)) and pairwise comparisons of these AUCs (95% CI) were computed in MedCalc. Receiver operating characteristic (ROC) curves for the three STOPANG models compared against a reference line indicating 50% AUC were displayed graphically. The best cut-points for ruling-in and ruling-out OSA, likelihood ratios and post-test probabilities for the STOPANG + WS model were calculated in Stata.

6.3 Results

A total of 122 patients completed the STOP-Bang tool. Raw BMI data (height and weight) was available for 121 patients. Ninety per cent of the 122 patients had a STOP-Bang score of ≥ 4 . The quality control check for oximetry data was classified as 'fail' for two patients. However, a sensitivity analysis conducted by removing these patients from the dataset and re-running the analysis, did not change the overall results.

Of the 122 patients, 65 had a likely diagnosis of OSA (hereafter referred to as OSA patients), giving a prevalence rate of 53.3%. The mean (SD) age and BMI of OSA patients were 48.8(12.6) years and 50.0(7.5) kg/m². OSA patients were significantly older, had higher BMIs and poorer oximetry readings when compared to patients without a likely diagnosis of OSA (hereafter referred to as non-OSA patients) (Table 6.1).

Table 6.1: Demographic data and prevalence of each STOPANG item, slow-walking speed and low physical activity levels for patients with and without a likely diagnosis of OSA.

	Likely diagnosis OSA Yes 65/122 (53.3%)	Likely diagnosis OSA No 57/122 (46.7%)	
Demographics:	Mean (SD)	Mean (SD)	Mean Difference (95% CI)
BMI	50.0 (7.5)	47.1 (7.0)	-2.9 (-5.6 to -0.3)
Age	48.8 (12.6)	42.7 (12.2)	-6.1 (-10.5 to -1.6)
Oximetry (dips per hour)	23.6 (21.3)	5.0 (2.5)	-18.6 (-24.2 to -13.0)
Mean Saturation	92.9 (2.4)	94.9 (1.8)	2.0 (1.2 to 2.7)
RDI	41.3 (21.4)	31.1 (17.0)	-10.2 (-17.2 to -3.2)
STOPANG+PA+WS:	N (%)	N (%)	% Difference (95% CI)
Reported snoring	64 (98.5)	52 (91.2)	-7.3% (-10.4% to 1.9%)
Epworth ≥ 12	29 (44.6)	25 (43.9)	-0.7 % (-19.6% to 18.3%)
Reported observed apnoeas	28 (43.1)	27 (47.4)	4.3% (-14.8% to 23.2%)
Hypertension	34	25	-8.4%

	(52.3)	(43.9)	(-27.2% to 10.9%)
Age (>50 years)	32 (49.2)	16 (28.1)	-21.1% (-38.2% to -2.2%)
Neck circumference (> 40cm)	63 (96.9)	45 (78.9)	-18.0% (-23.4% to -5.1%)
Gender (Male)	24 (36.9)	12 (21.1)	-15.8% (-31.3% to 2.0%)
Low physical activity level	42 (64.6)	38 (66.7)	2.1% (-16.3% to 19.9%)
Slow-walking speed	54 (83.1)	35 (61.4)	-21.7% (-36.5% to -4.2%)

*BMI data N = 121; RDI = respiratory disturbance index; PA = low physical activity level; WS = slow-walking speed; CI = confidence interval

OSA patients also had a higher prevalence of 'yes' responses to all STOPANG items except 'reported observed apnoeas', which were higher in the non-OSA patients. Only the STOPANG items for age and neck circumference were significantly different between the two groups (% difference, 95% CI: age = -21.1%, -38.2 to -2.2, neck circumference = -18.0%, -23.4 to -5.1). A slow-walking speed was reported significantly more in OSA patients than non-OSA patients (% difference, 95% CI: 21.7%, 4.2 to 36.5). A greater percentage of non-OSA patients than OSA patients reported low physical activity levels (Table 6.1).

The STOPANG + WS model had the highest AUC (0.697, 95% CI 0.607 to 0.777) (Table 6.2) and this was significantly greater than the AUC for the other two models (difference in AUC, 95% CI: STOPANG vs. STOPANG + WS model = 0.0547, 0.0184 to 0.0909, STOPANG + WS vs. STOPANG + PA model = 0.0727, 0.0219 to 0.124) (Table 6.3; Figure 6.1). The STOPANG + PA model had the lowest AUC (0.624, 95% CI 0.532 to 0.710) (Table 6.2).

Table 6.2: ROC curve performance for the three STOPANG models

Model	AUC	95% CI
STOPANG	0.642	0.550 to 0.727
STOPANG + WS	0.697	0.607 to 0.777
STOPANG + PA	0.624	0.532 to 0.710

*ROC = receiver operating characteristic curve; AUC = area under the ROC curve; WS = slow-walking speed; PA = low physical activity level; CI = confidence interval

Table 6.3: Pairwise comparison of ROC curves for the three STOPANG models

Model	Difference in AUC	95% CI
STOPANG v STOPANG + WS	0.0547	0.0184 to 0.0909
STOPANG v STOPANG + PA	0.0181	-0.0213 to 0.0575
STOPANG + WS v STOPANG + PA	0.0727	0.0219 to 0.124

*ROC = receiver operating characteristic curve; CI = confidence interval; WS = slow-walking speed; PA = low physical activity level

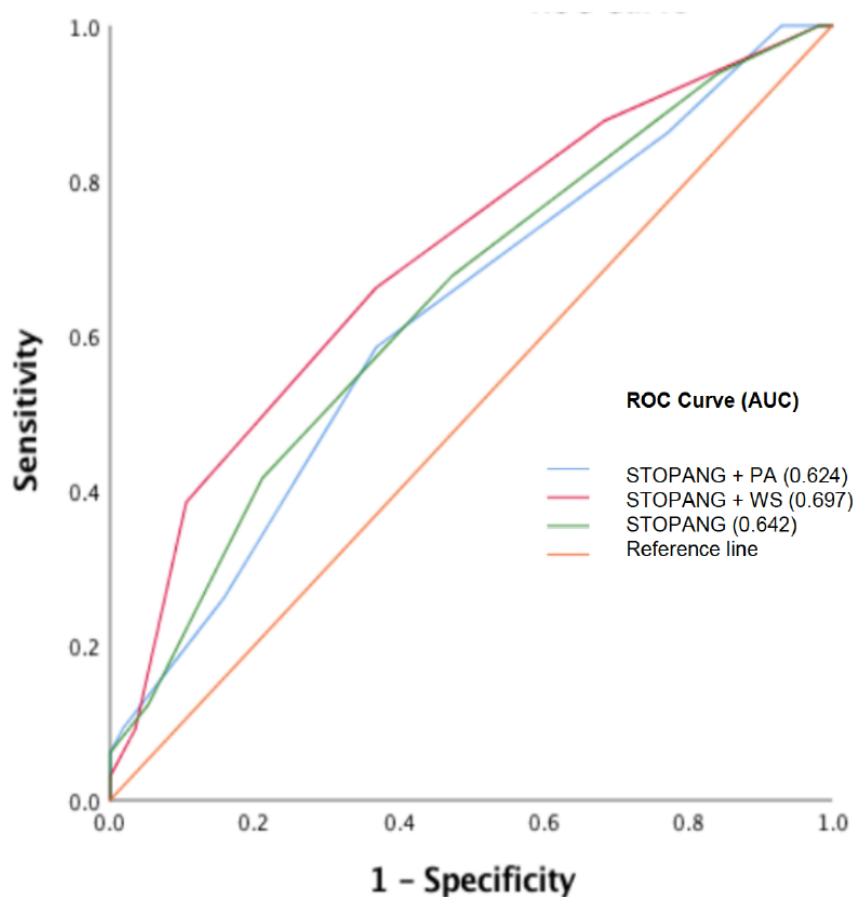


Figure 6.1: Receiver operating characteristic curves for the three STOPANG models compared against a reference line indicating 50% AUC (WS = slow-walking speed; PA = low physical activity level; AUC = area under the ROC curve)

Examining the STOPANG + WS model, it was found that the best cut-point for ruling-in OSA was a score of ≥ 6 (Table 6.4). The associated post-test probability indicated that a patient with a STOPANG + WS score ≥ 6 would have a 79% chance of having OSA. The best cut-point for ruling-out OSA was a score of ≤ 3 (Table 6.4). The associated post-test probability indicated that a patient with a STOPANG + WS score ≤ 3 would have a 28% chance of having OSA.

Table 6.4: Best cut-points for ruling-in and ruling-out OSA, likelihood ratios and post-test probabilities for the STOPANG + WS model

Ruling in	+ Likelihood ratio (95% CI)	Post-test probability (95% CI)
≥ 6	3.65 (1.6 to 8.3)	79% (62% to 89%)
Ruling out	- Likelihood ratio (95% CI)	Post-test probability (95% CI)
≤ 3	0.39 (0.2 to 0.8)	28% (17% to 44%)

6.4 Discussion

In this chapter, it was found that a question pertaining to slow-walking speed significantly increased the STOPANG models screening performance in weight-loss surgery patients (increasing the AUC from 0.64 to 0.70). The best cut-points for ruling-in and ruling-out OSA for the STOPANG + WS model were ≥ 6 and ≤ 3 respectively.

The high prevalence of OSA (likely diagnosis OSA ‘yes’ = 53.3%) was in keeping with the literature for this population group in which prevalence rates of > 50% are frequently reported (Chung, Abdullah and Liao, 2016; de Raaff, de Vries and van Wagenveld, 2018). As expected, OSA patients had a higher prevalence of ‘yes’ responses to most of the STOPANG items compared to non-OSA patients (Table 6.1). However, the STOPANG item pertaining to ‘reported observed apnoeas’ was higher in the non-OSA patients (Table 6.1). Nagappa *et al.*, (2017a) suggest that this question may not be captured accurately if a patient’s bed partner is not present. Difficulties in answering this screening question may explain the current finding. This highlights the importance of using questions in screening tools that can be easily and accurately answered by patients.

Self-reported walking speed has been shown to be a good marker of measured walking speed in older adults (Syddall *et al.*, 2015) and is an easily answered question with good response rates reported (Suri *et al.*, 2015). In this chapter, it was found that significantly more OSA patients than non-OSA patients reported a slow-walking speed (% difference, 95% CI: 21.7%, 95% CI 4.2 to 36.5) (Table 6.1). The fact that the prevalence difference for the walking speed item in this chapter was larger than those observed for any of the STOPANG items is highly encouraging as it suggests that slow-walking speed may be able to better differentiate between people with and without OSA than current clinical screening questions. This finding also concurs with the theme throughout the thesis so far, which consistently supports a relationship between being less active and an increased incidence of SDB (Peppard and Young, 2004; Awad *et al.*, 2012; Simpson *et al.*, 2015; Suri *et al.*, 2015; Kline *et al.*, 2017).

Promisingly, when the walking speed item was added to the STOPANG model it improved the AUC from 0.64 to 0.70 (Table 6.2). This AUC was significantly greater than the AUCs for the other two screening methods (Table 6.3). Again, the data support the clinical utility of a walking speed question and suggest that adding a walking speed item to current screening protocols may help to increase identification of patients with OSA prior to weight-loss surgery. This would allow for an appropriate care programme to be initiated prior to surgery, potentially decreasing the risk of OSA-related complications during the perioperative period (Riad and Chung, 2013). Identification of higher-risk patients during this time would also allow clinicians to institute additional measures to manage the patient's OSA during the perioperative period, such as planning for increased monitoring and being more cautious of medications used during anaesthesia (OSA patients may have an increased sensitivity to perioperative opioids and sedation) (Danjoux and Habgood, 2016). This would facilitate a safer and more efficient perioperative journey, beneficial to the patient, their support team and the NHS. The clinical pathway for

identifying OSA in weight-loss surgery patients at JCUH is provided in figure 6.2.

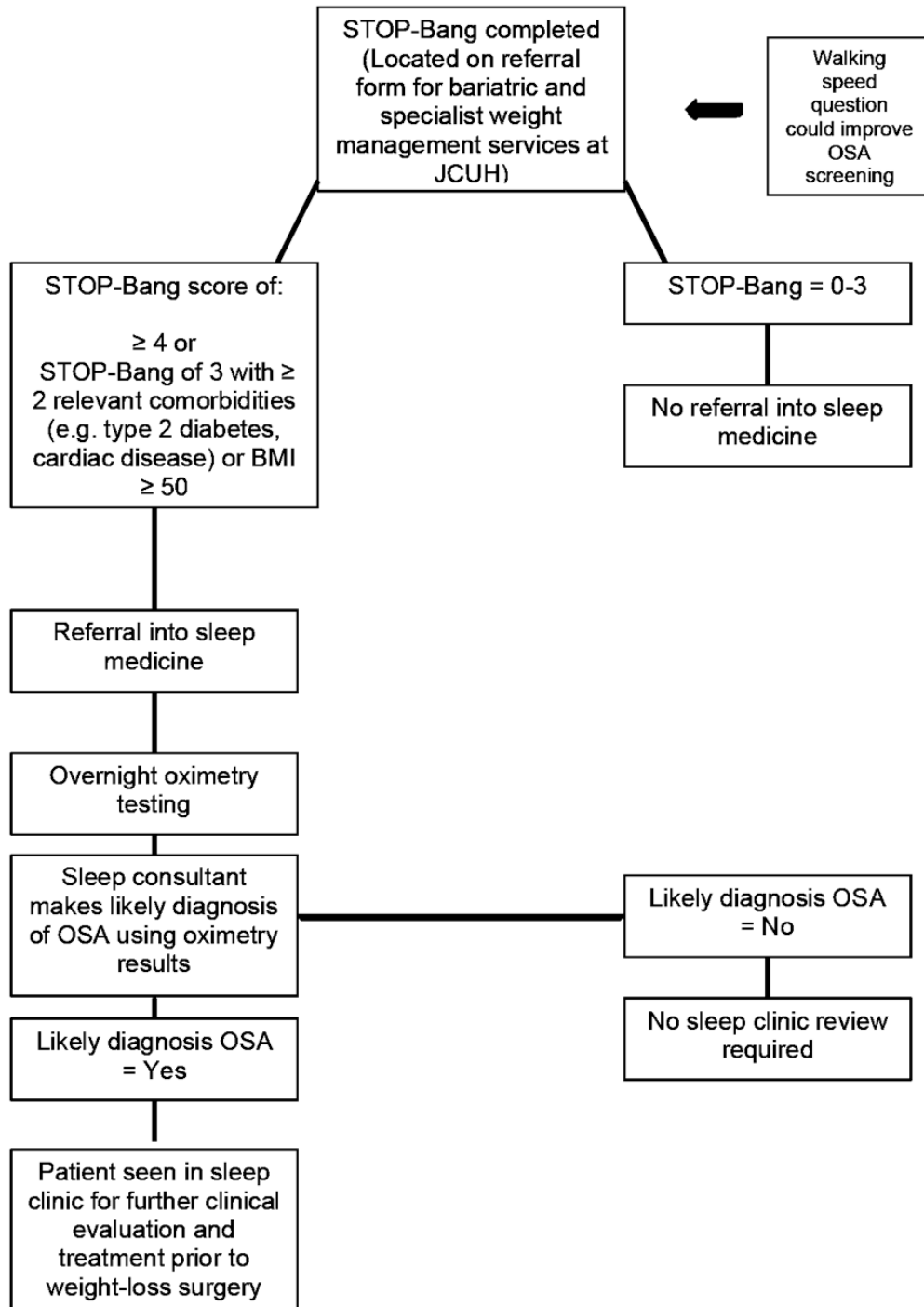


Figure 6.2: Clinical pathway for identifying OSA in bariatric and specialist weight management patients prior to weight-loss surgery at JCUH

Although the size of the STOPANG + WS's AUC was classified at the lower end of 'fair' using suggested interpretations from the literature (AUC: ≥ 0.9 = excellent, ≥ 0.8 = good, ≥ 0.7 = fair and < 0.7 = poor) it is still considered to have potential as a screening tool, especially as the 95% confidence interval for the AUC (0.61 to 0.78) did not include the null-value (AUC = 0.5) (Youngstrom, 2014). Higher AUCs are desirable for clinical screening tests, yet putting the current work into context, AUCs for clinical OSA screening tools are often not in the categories of 'good' or 'excellent' using the suggested thresholds stated above, with research on-going to improve their screening utility (Pataka *et al.*, 2014). The STOP-Bang variants, which have been researched in an attempt to improve its diagnostic performance by adding more items e.g. serum bicarbonate level (Chung *et al.*, 2013), an 'apple-body type' (Sangkum *et al.*, 2017) or by changing the way the tool is scored (Nahapetian *et al.*, 2016), have still only yielded AUCs ≤ 0.8 . For example, using a large dataset (N > 1500) from the Sleep Heart Health Study, Nahapetian *et al.*, (2016) examined whether using different methods for scoring the STOP-Bang (a 'weighted model' and a 'continuous model') would improve its performance. These authors found that the AUC for the conventionally scored STOP-Bang, the 'weighted model' and the 'continuous model' were 0.71, 0.69 and 0.74 respectively (Nahapetian *et al.*, 2016).

An advantage of the current STOPANG + WS model is that unlike these aforementioned STOP-Bang models, it omits the original BMI item, which has a threshold value of 35 kg/m². As this item is usually positive for the majority of bariatric patients, it is proposed that it is inappropriate for use in this population group. Therefore, the new STOPANG + WS model is considered a more appropriate tool for use with these patients.

Given the promising results for the walking speed item, it was interesting that a similar trend was not seen with the question regarding physical activity levels (a slightly decreased prevalence of low-physical activity levels was observed in the OSA patients compared to non-OSA patients and the addition of the physical activity item decreased the STOPANG's ROC performance) (Tables 6.1 and 6.2 respectively). Self-reporting of

physical activity levels has been identified as problematic in the literature with incongruence between objectively measured and subjectively reported figures (Bond *et al.*, 2010). This may explain the unexpected findings for this variable and again emphasises the need to really consider the items carefully (e.g. validity, ease of measurement) when designing a screening tool in order to optimise its diagnostic utility.

After further examining the STOPANG + WS model it was found that the best cut-point for ruling OSA in was a score of ≥ 6 (Table 6.4). The associated likelihood ratio of 3.65 (95% CI 1.6 to 8.3) indicated that a score of ≥ 6 increased the probability of disease to 79% (95% CI 62 to 89) (post-test probability) (Table 6.4). Although the likelihood ratio was not substantial (based on guidelines from the literature a likelihood ratio > 10 = large), the model's best ruling-in cut-point raised the post-test probability sufficiently high enough to warrant further testing (Deeks and Altman, 2004). The best cut-point for ruling OSA out was a STOPANG + WS score of ≤ 3 , which decreased the probability of OSA to 28% (95% CI 17 to 44) (post-test probability) (Table 6.4). However, this probability is still too high to rule-out disease with confidence, indicating an area of performance where this model may need further work to optimise its screening utility (Deeks and Altman, 2004).

Finally, before drawing conclusions, the strengths and limitations of the current chapter must be discussed. Firstly, this work is highly novel. The effect of a physical activity/walking speed-related question on the STOP-Bang's diagnostic performance has not been previously examined in the literature. A second strength is that because there was no variance in the STOP-Bang's item for BMI in this patient group, it was excluded from the analyses. Including BMI may have compromised the results, as all patients were positive for this item. There are also limitations of this work to consider. The sample size was relatively small ($N = 122$), diagnosis of OSA was only a likely diagnosis based on oximetry data (not full PSG) and the different severity levels of OSA were not analysed.

6.5 Conclusion

Building on the work conducted in chapter four, this chapter explored whether the addition of one of two simple and easily reported questions relating to physical activity and everyday walking speed could improve the diagnostic performance of a currently used screening tool for OSA (STOP-Bang). The findings suggest that a slow-walking speed question has the potential to improve the diagnostic utility of the STOPANG tool in weight-loss surgery patients. The new STOPANG + WS model, which omits the BMI item, is also considered to be a more appropriate screening tool for OSA in bariatric populations. Further work using full PSG and larger samples is needed to build on these preliminary yet promising results.

Chapter Seven: Patient and public involvement: An exploration of views regarding exercise and physical activity amongst weight-loss surgery patients with obstructive sleep apnoea

7.1 Introduction

Weight-loss surgery patients with OSA are at an increased risk of perioperative complications (e.g. cardiopulmonary complications), which may require admission to high dependency or intensive care units, increase the length of hospital stay and even result in mortality (Dawson, Singh and Chung, 2016). In the current NICE guidelines, CPAP is recommended for all patient groups diagnosed with OSA (NICE, 2008; Danjoux and Habgood, 2016). Patients newly diagnosed prior to surgery should be treated as per NICE guidance with CPAP commenced 8-12 weeks preoperatively to reduce perioperative risks (NICE, 2008; Danjoux and Habgood, 2016). Although weight-loss surgery patients may be informed of the importance of CPAP, compliance is poor (Thomas *et al.*, 2013; Luyster *et al.*, 2016). Alternative management strategies are needed to reduce patient risk and potential economic costs that may result from OSA-related complications (Chung *et al.*, 2013; Danjoux and Habgood, 2016).

As has been previously highlighted within the thesis, exercise can reduce the severity of OSA, independent of any weight-loss that may also occur (Iftikhar, Kline and Youngstedt, 2014; Suri *et al.*, 2015; Iftikhar *et al.*, 2017). Therefore, exercise prior to weight-loss surgery may improve OSA severity and also address the low levels of cardiorespiratory fitness reported in this patient group, which in itself can increase perioperative risk (McCullough *et al.*, 2006; Carver *et al.*, 2011; Tew *et al.*, 2018). Emerging evidence also suggests that weight loss alone may not cure OSA (Joosten, Hamilton and Naughton, 2017). This further supports the need for alternative or adjunct

therapies such as exercise, which also offers many additional physiological and psychological benefits (Iftikhar, Kline and Youngstedt, 2014).

However, guidance for providing safe and effective exercise prior to elective major surgery is limited and further trials are needed to build the evidence base (Tew *et al.*, 2018). Consequently, in chapter eight of this thesis, a protocol for a feasibility RCT examining the benefits of exercise for obese people with OSA who undergo weight-loss surgery is proposed.

It is important to involve the public in the research process to increase the relevance, quality and impact of this trial as they can provide unique perspectives that cannot be gained from the research team and clinicians alone (INVOLVE, 2012; Brett *et al.*, 2014; National Institute for Health Research (NIHR), 2014; Pandya-Wood, Barron and Elliott, 2017). INVOLVE (2012, p. 6) define public involvement in research as “research being carried out ‘with’ or ‘by’ members of the public rather than ‘to’, ‘about’ or ‘for’ them”. The term ‘public’ is used to include “patients, potential patients, carers and people who use health and social care services as well as people from organisations that represent people who use services” (INVOLVE, 2012, p. 6). The public involvement work (referred to throughout the thesis as PPI), which was conducted to support the feasibility study, is presented in this chapter. The aim of the PPI work was to explore OSA patients’ views towards exercise in order to inform a protocol for a feasibility RCT examining the benefits of exercise for obese people with OSA who undergo weight-loss surgery.

7.2 Methods

7.2.1 Participants

A questionnaire-based assessment of patients’ opinions about exercise training was undertaken in the sleep clinic at JCUH in July 2016. A convenience sample of five patients (four males, one female) who were being considered for weight-loss surgery (three patients referred from the

specialist weight management services (SWMS) pathway and two patients referred from the bariatric pathway) and also had OSA completed the PPI work. Formal ethical approval was not needed for this work but Sophie Suri, a postgraduate researcher at Teesside University looking at the topic of exercise and OSA, possessed a research passport for JCUH (NIHR, 2014) (Appendix 11). All data was collected anonymously.

7.2.2 Data Collection

At the beginning of each patient's appointment in the sleep clinic, they were asked by the clinician if they would be willing to answer questions from a short questionnaire about their opinions regarding a potential exercise intervention prior to weight-loss surgery. If patients were agreeable, these questions were asked at the end of their clinical appointment by Sophie Suri. All questions were asked in a clear and sensitive manner after establishing a brief rapport with the patient (Pandya-Wood, Barron and Elliott, 2017).

Members of the research team developed the questionnaire, which was based on a patient questionnaire previously used on surgical patients with lung cancer in the development of a study protocol. However, the questions were edited accordingly for focus on OSA, weight-loss surgery and physical activity. The Research and Development team within South Tees Hospitals NHS Foundation Trust (STHNHSFT) approved the final questionnaire before its use with patients.

The questionnaire captured the patient's sex and weight-loss surgery pathway (SWMS or bariatric) and consisted of eight short closed questions (e.g. *'How important do you think increasing your levels of exercise and fitness might be for improving your current health status?'* Possible answers: very important, important, somewhat important or not important at all). Patients were asked to choose one response for each question with the exception of question seven, which allowed for multiple responses. Closed questions were used to facilitate the collection of simple, structured data

during a busy clinical period (Gratton and Jones, 2004). After the closed questions, a filter question was asked. This filter question asked for a 'yes/no' answer with additional information required if the patient's response was 'no'. Finally, an open question was asked, and patients were provided with an opportunity to add any further comments or suggestions. The full questionnaire is presented in Appendix 12.

7.2.3 Data analysis

Sophie Suri analysed the data. For closed questions, the frequency of each response option was recorded and reported for each question. For open questions, the variety of responses provided for each question were all recorded and reported. This was feasible given the small sample size. An overall summary and individual question summaries were then formulated. No further data analysis was completed.

7.3 Results

7.3.1 Overall Summary

All five patients thought that increasing their levels of exercise and fitness was important for improving their current health status and were willing to be part of an interval-based exercise study, in either arm of the trial, provided all travel expenses were paid. There was also a positive overall consensus for keeping an activity log/wearing a pedometer to track daily physical activity levels.

All patients stated that they would like to improve their weight, health-related quality of life and symptoms of OSA in the study. Increasing physical activity, exercise capacity and reducing the length of hospital stay after surgery were also prioritised as important outcomes by the patients.

Three out of five patients stated that they would want to provide study feedback in a telephone interview with the researcher. Two out of five patients said they would prefer to disclose this information in a researcher-led interview or focus group.

Patients suggested that they thought appropriate questions to ask in the study feedback should be related to a) how happy they were with the exercise, b) whether they enjoyed the intervention, c) how they felt during and directly after the exercise session (and in the immediate longer term e.g. improved quality of life) and d) if the exercise caused them any pain or dizziness. Table 7.1 presents the patient responses to the multiple-choice questions in the public involvement questionnaire.

Table 7.1: Patient responses to multiple choice questions in the public involvement questionnaire

Question	Potential responses	Patient responses (N = number of patients)
1. How important do you think increasing your levels of exercise and fitness might be for improving your current health status?	Very important Important Somewhat important Not at all important	N = 4/5 N = 1/5 N = 0/5 N = 0/5
2. How would you feel about doing some supervised exercise lasting for a maximum of 1 hour, twice a week, at Teesside University if your travel expenses were paid for?	Fine A little concerned Very concerned I wouldn't do it	N = 4/5 N = 1/5 N = 0/5 N = 0/5
3. How would you feel if this exercise was done in short "chunks" lasting 30-60 seconds where you would become out of breath but then there would be some rest periods in between?	Fine A little concerned Very concerned I wouldn't do it	N = 5/5 N = 0/5 N = 0/5 N = 0/5
4. Would you be willing to keep a written log of how much physical activity/exercise you do during every-day activities?	Yes No	N = 3/5 N = 0/5

		NB: 1 patient would possibly consider keeping a log; 1 patient willing to record activity if alternative recording method provided
5. Would you be willing to wear a pedometer type tracker (worn on the waist) to measure how much physical activity/exercise you do during every-day activities?	Yes No	N = 4/5 N = 0/5 NB: One patient was unsure due to using a mobility aid
6. Anyone who is involved in this study would have about a 33% chance of being allocated to a no-exercise "control" group rather than the group who receive the exercise training. Here, you would receive all the treatment you would normally get, but you would not be given any supervised exercise. However, health measurements would be obtained from you at various times before and after your surgery. Would this affect your willingness to be involved in the study?	Yes No	N = 5/5 N = 0/5
7. Which health measures (you can choose <i>more than 1</i>) would you want to improve in the study?	Symptoms of sleep apnoea	N = 5/5

	Length of hospital stay after surgery	N = 2/5
	Exercise capacity (fitness)	N = 4/5
	Your weight	N = 5/5
	Health related quality of life (including feelings of tiredness, feelings of being in control and feelings of anxiety and/or depression)	N = 5/5
	Physical activity (how active you are)	N = 4/5
8. During a study, feedback from patients about the exercise programme is very important. How would you feel most comfortable providing us		N = 1/5

with this information if you were in this position?	the researcher)	
9. Hypothetically, would you be interested in participating in a study of this kind? If NO, could you explain reasons why you would not want to participate?	Telephone interview (the researcher will phone you at a convenient time)	N = 3/5
	Focus group (a group discussion with other patients and the researcher)	N = 1/5
	Survey (a written survey completed at your postoperative clinic appointment)	N = 0/5
	Yes No	N = 5/5 N = 0/5

7.3.2 Question summaries

Question One:

‘How important do you think increasing your levels of exercise and fitness might be for improving your current health status?’

All five patients thought that increasing their levels of exercise and fitness was important or very important for improving their current health status.

Question Two:

‘How would you feel about doing some supervised exercise lasting for a maximum of one hour, twice a week, at Teesside University if your travel expenses were paid for?’

Four patients were willing to attend Teesside University to do some supervised exercise lasting for a maximum of one hour, twice a week, providing that travel expenses were paid. One patient said they would consider the exercise intervention if travel was fully organised (the patient did not drive and struggled with mobility) and if their current physiotherapist was happy with the intervention.

Question Three:

‘How would you feel if this exercise was done in short “chunks” lasting 30-60 seconds where you would become out of breath but then there would be some rest periods in between?’

All five patients felt happy to do exercise in short “chunks” lasting 30-60 seconds where they would become out of breath but then there would be some rest periods in between.

Question Four:

‘Would you be willing to keep a written log of how much physical activity/exercise you do during every-day activities?’

Three patients were happy to keep a written log regarding their physical activity during every-day activities. One patient said they would possibly consider keeping a log. One patient who was unable to write said they would be happy to keep a log if there was a format that allowed them to do this.

Question Five:

‘Would you be willing to wear a pedometer type tracker (worn on the waist) to measure how much physical activity/exercise you do during every-day activities?’

Four patients said they would be willing to wear a pedometer-type tracker (worn on the waist) to measure their physical activity/exercise levels during every-day activities. One patient used a mobility aid and did not think this would be applicable to their situation.

Question Six:

‘Anyone who is involved in this study would have about a 33% chance of being allocated to a no-exercise “control” group rather than the group who receive the exercise training. Here, you would receive all the treatment you would normally get, but you would not be given any supervised exercise. However, health measurements would be obtained from you at various times before and after your surgery. Would this affect your willingness to be involved in the study?’

All five patients were happy to be part of the control group if they were not part of the exercise group.

Question Seven:

‘Which health measures (you can choose more than one) would you want to improve in the study?’

Five patients said they would like to improve their weight, health-related quality of life and symptoms of OSA in the study. Four patients said they would like to improve their physical activity and exercise capacity and two patients wanted to reduce the length of hospital stay after surgery.

Question Eight:

‘During a study, feedback from patients about the exercise programme is very important. How would you feel most comfortable providing us with this information if you were in this position?’

Patients said they would prefer to give study feedback in a telephone interview (three patients), a focus group (one patient) or a face-to-face interview (one patient) with the researcher.

Question nine:

‘Hypothetically, would you be interested in participating in a study of this kind?’

All five patients said they would hypothetically be interested in taking part in a study of this kind.

7.3.3 Further patient comments

Patients suggested that they thought appropriate questions to ask in the feedback part of the study should concern:

a) Whether they were happy with and enjoyed the type of exercise

- b) How they felt during and directly after the exercise session
- c) Whether the exercise caused them any pain or dizziness
- d) Whether they felt better in the longer term (e.g. improved quality of life)

One patient was concerned about the length of each exercise session. They felt unsure as to whether they would be able to complete a full session but said they would be willing to do what they could. NB: It was noted that patients in this population group had other health conditions/comorbidities.

7.4 Discussion

In this chapter, OSA patients' views towards exercise were explored in order to inform a protocol for a feasibility RCT examining the benefits of exercise for obese people with OSA who undergo weight-loss surgery.

The preliminary logistics of the trial were well received by the patients. A RCT involving two supervised hour-long exercise sessions, twice weekly, at Teesside University appears to be a feasible design framework for a protocol provided that travel expenses are covered. Also, all patients were happy with the proposed interval design. One patient had concerns regarding mobility issues, indicating an area for consideration regarding modes of exercise and potential venues in the protocol design in chapter eight. The same patient also expressed concern regarding the acceptability of the exercise intervention by their physiotherapist. Developing information leaflets for patients to give to members of their care team prior to study enrolment may be an option to explore to facilitate multidisciplinary team guidance and support.

When choosing outcome measures for an exercise intervention, it is imperative that they reflect the benefits that patients want to see from their participation. Weight, health-related quality of life and symptoms of OSA were unanimously agreed as important trial outcomes by the patients, with four out of the five patients also wanting to increase their fitness and physical

activity levels. Therefore, it is important to include these outcomes in the protocol in order to increase trial relevance and 'success' from both patient and clinical perspectives (Yordanov, Dechartres and Ravaud, 2018). Only two patients indicated that length of hospital stay after surgery was a health measure they wanted to improve. Including this outcome measure in the protocol, which does not require great expense or time to document, is still considered important as it could add value to the research for the wider population group. Such data also provides value when viewing the research from an economic perspective.

The measurement of one of the proposed trial outcomes (daily physical activity levels) was identified as a potential concern during the PPI work. The written format of recording physical activity levels was brought to attention by one patient who was not able to write. Measurement of daily steps using a pedometer-type tracker worn on the waist was also identified as problematic by one patient who used a mobility aid. Consequently, alternative subjective (e.g. voice recorder option) and objective methods of recording activity need to be investigated in order to reliably, accurately and sensitively capture daily physical activity levels in this population group (Warms, 2006). These alternative methods could be explored in the feasibility trial itself.

The patients' initial awareness of the importance of exercise for improving their health status and their desire to improve their physical activity levels was highly encouraging. However, patients awaiting bariatric surgery are reported to be quite sedentary, with physical and psychological barriers to exercise often reported (King and Bond, 2013; Zabatiero *et al.*, 2016). Therefore, careful consideration is needed in the trial design regarding how to remove/work around as many barriers to exercise as possible and help translate this patient group's knowledge and desire into action.

The Questionnaire data suggested that one of these barriers to exercise is physical health, a finding supported by previous research with obese adults (King and Bond, 2013; McIntosh, Hunter and Royce, 2016). As recognised in

the PPI work, weight-loss surgery candidates often have physical limitations due to the presence of comorbidities (Guh *et al.*, 2009). Consequently, particular attention needs to be given to the design of the exercise programme (e.g. employing lower impact exercise options) to increase trial safety, accessibility and support-desired outcomes (Hoffmann *et al.*, 2016).

A further barrier to exercise, which was addressed by one patient, was concern about their ability to complete the exercise regime due to poor physical fitness, a view not uncommon in the literature (King and Bond, 2013; McIntosh, Hunter and Royce, 2016). Therefore, progressing exercise gradually, providing increased support and setting achievable targets and starting points to help patients gain confidence are highly important design considerations. Addressing these points may also optimise enjoyment and limit pain, which were highlighted as valued feedback factors by the patients regarding exercise.

Prior to concluding the findings from this chapter, the limitations of the PPI work conducted must be discussed. First of all, the questionnaire method employed to obtain the required information did not allow patients to respond in-depth about their opinions on exercise and physical activity (Gratton and Jones, 2004). However, it is felt that enough information was captured to inform the preliminary stages of the design process. A second potential limitation is the fact that the PPI work was completed by a male dominated convenience sample. Although this may limit the ability to generalise from the results, it is argued that the current work is still highly beneficial to informing the feasibility study for the following reasons; a) Patients were only being asked for their opinions on exercise and had little reason to not provide this information, b) the views obtained were from a directly relevant patient group and c) the results obtained did corroborate with past research in this area (Gratton and Jones, 2004; King and Bond, 2013; McIntosh, Hunter and Royce, 2016).

7.5 Conclusion

The PPI work conducted in this chapter has provided invaluable information to inform the concluding chapter of the thesis, which presents a protocol for a feasibility RCT examining the benefits of exercise for obese people with OSA who undergo weight-loss surgery. From the data collected, it appears that a supervised interval-based exercise RCT at Teesside University is acceptable in this patient group. However, it is important that the potential patient barriers and other highlighted considerations from this work are incorporated into the following protocol to maximise trial success and ultimately enhance research impact.

Chapter Eight: The benefits of exercise for obese people with obstructive sleep apnoea who undergo weight-loss surgery: A protocol for a feasibility trial

8.1 Introduction

Weight-loss surgery candidates have a high risk of OSA (Chung, Abdullah and Liao, 2016), adhere poorly to current treatment (CPAP) (Thomas *et al.*, 2013) and often present with low levels of cardiorespiratory fitness (McCullough *et al.*, 2006). These factors increase this clinical population's perioperative risk (e.g. from OSA-related complications and decreased functional capacity), which could adversely affect patient health and potentially lead to an increased economic burden to healthcare (Dawson, Singh and Chung, 2016; Tew *et al.*, 2018).

The beneficial effects of exercise on cardiorespiratory fitness and OSA severity (chapter three) provide a platform for exploration to address the above concerns in a 'prehabilitation' context (Iftikhar, Kline and Youngstedt, 2014; Iftikhar *et al.*, 2017). Prehabilitation refers to "the process of enhancing an individual's functional capacity to enable them to withstand a forthcoming stressful event" such as major elective surgery (Snowden and Minto, 2015. p.187). Improving the functional capacity and OSA severity of weight-loss surgery patients through a structured, purposeful preoperative exercise programme may reduce perioperative complications, reduce the length of hospital stay and engage these patients in a longer-term preventative model of healthcare (Speake *et al.*, 2016; NHS, 2017; Tew *et al.*, 2018).

Exercise training has been reported to improve OSA severity in non-bariatric patients (Iftikhar, Kline and Youngstedt, 2014; Iftikhar *et al.*, 2017) and the cardiorespiratory fitness of bariatric patients (Carver *et al.*, 2011; Onofre *et al.*, 2017.) It is unknown at present whether exercise can improve OSA severity and cardiorespiratory fitness in weight-loss surgery patients with the disorder. Randomised controlled trials with specifically designed preoperative

exercise training programmes in different clinical populations have been called for to bridge this gap (Tew *et al.*, 2018). Therefore, in this chapter of the thesis, a protocol for a feasibility RCT examining the benefits of exercise for obese people with OSA who undergo weight-loss surgery is presented.

Feasibility studies are viewed as an integrated part of pilot work by some authors and institutions (NIHR, 2016). However, the NIHR view feasibility and pilot studies as distinct separate activities, with feasibility work driven by information needs and predominantly concerned with estimating unknown parameters (e.g. recruitment, adherence and retention figures) to examine whether a full-scale trial is viable (NIHR, 2016). Under the NIHR definition, pilot studies involve a small scale testing of the actual larger trial to determine if key study elements run smoothly (NIHR, 2016). This work will be categorised as a feasibility study (adopting the NIHR definition) as the main aim is to estimate important parameters to inform the design of a subsequent definitive trial.

8.1.1 Aim

The primary aim of this chapter was to develop a sound protocol, informed by information collected in previous chapters and from the literature base in general, to assess the feasibility and acceptability of delivering an exercise intervention to obese patients with OSA who undergo weight-loss surgery.

8.1.2 Ultimate objectives that inform the protocol design

1. Determine the variability (standard deviation) of potential outcome measures for a subsequent definitive trial
2. Assess the feasibility of measuring the proposed outcome measures
3. Examine feasibility and acceptability parameters to assess study viability (e.g. number of eligible patients; recruitment, retention and adherence figures)
4. Examine the acceptability by clinicians of delivering this trial in the existing clinical pathway for weight-loss surgery patients with OSA

5. Assess study safety (number of adverse events directly related to the intervention)
6. Determine realistic study timescales for a full trial

8.2 Methods

8.2.1 Study design

This work will be a single-centre, two-arm, parallel-group, randomised controlled feasibility study (Figure 8.1). The study will be a collaboration between people from two institutions; one clinical and one academic.

8.2.2 Participants

Weight-loss surgery patients who have been identified as having a high likelihood of OSA from preoperative screening/testing are seen in the sleep clinic at the clinical institution for formal diagnosis and treatment initiation. A researcher will approach weight-loss surgery patients who potentially meet the study inclusion criteria directly after this appointment and ensure they meet all inclusion criteria. Patients interested in the study will be provided with a participant information sheet. Additional information leaflets for patients to give to members of their care team prior to study enrolment will also be made available. A researcher will contact (by telephone) patients who have expressed interest in participation at the clinic. Patients willing to take part in the study will be scheduled for initial cardiopulmonary exercise testing (CPET) once verbal consent is gained.

All CPET will be conducted at the clinical institution under strict supervision one week prior to baseline testing. CPET will follow protocols similar to those used previously with this population group (Hennis *et al.*, 2012; Lanzi *et al.*, 2015). The CPET will act as a final screening measure and will also facilitate exercise prescription (Figure 8.1).

Study inclusion criteria:

- ≥ 18 years old
- Weight-loss surgery patient
- Diagnosed using routine clinical testing procedures as having moderate to severe OSA ($AHI \geq 15$)
- CPAP therapy has been initiated at preoperative assessment in the sleep clinic
- Meet no study exclusion criteria as determined using internationally recognised guidelines for exercise testing and prescription (The American College of Sports Medicine (ACSM), 2014).

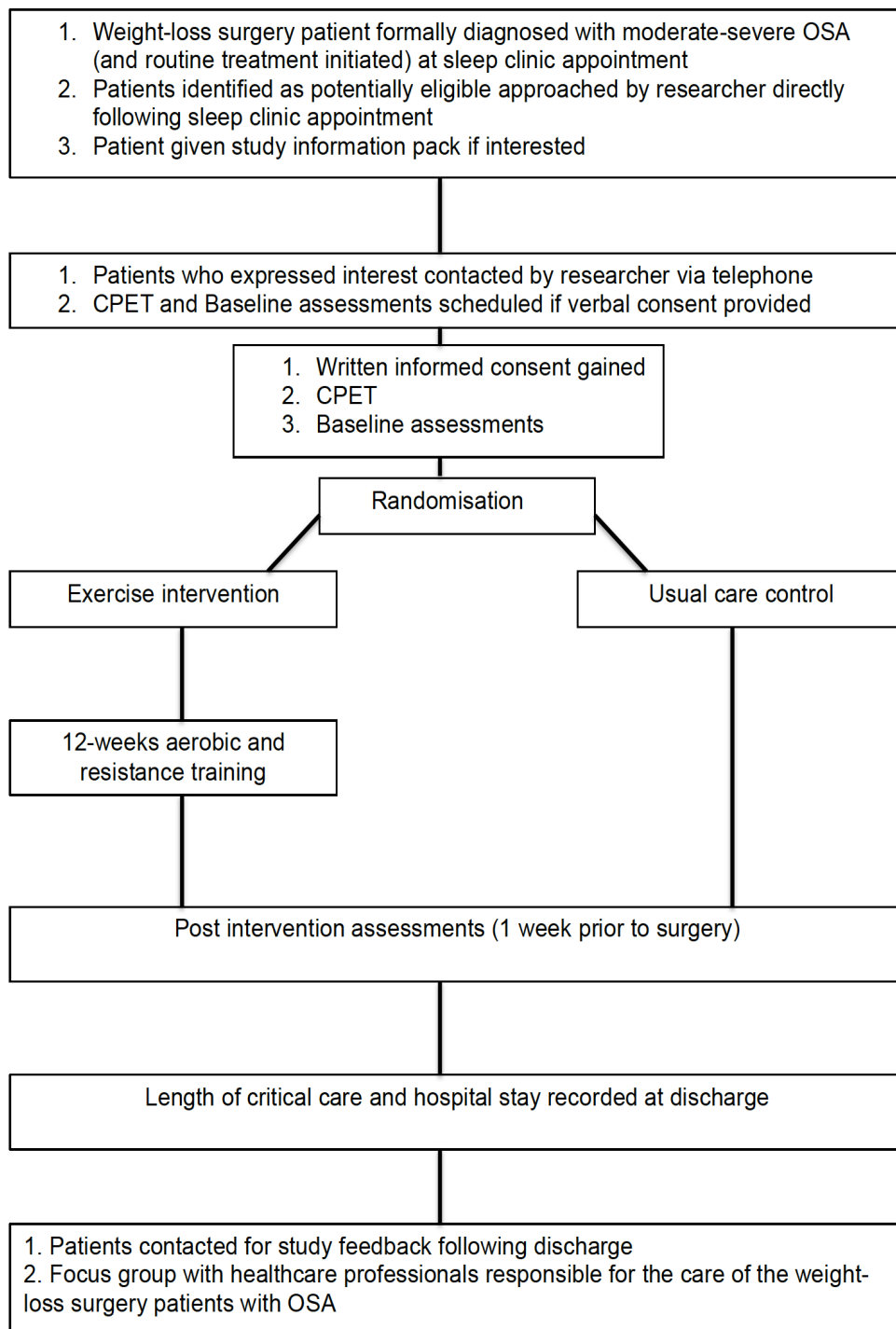


Figure 8.1: Study flow-chart (CPET = cardiopulmonary exercise testing)

8.2.3 Randomisation and sample size

After CPET and baseline assessments, patients will be randomly allocated 2:1 (to place emphasis on the exercise intervention process) to intervention (usual care and exercise) or usual care control (no exercise). Minimisation will be used to ensure balance across trial arms for important prognostic factors such as age and sex. The study statistician will conduct the minimisation process remotely via email. Previous PPI work (chapter seven) indicated that patients are willing to be randomised to either group in this study.

Sample sizes between 24 and 50 have been suggested for use in pilot studies (Julious, 2005; Sim and Lewis, 2012). Therefore, the current study will recruit 42 patients (28 patients in the intervention arm and 14 patients in the usual care control arm). Approximately 100-150 bariatric patients are screened annually at the clinical institution for OSA and prevalence rates of moderate to severe OSA are > 45% in this population group (Kositanurit *et al.*, 2018). An 18-month period for recruitment is deemed appropriate to achieve a total sample size of 42 patients.

8.2.4 Exercise intervention

The exercise intervention will take place in an easily accessible location at the academic institution, which patients confirmed as acceptable in the PPI work (chapter seven). Safety governance measures will be strictly adhered to throughout the programme (see section 8.4). This programme has been informed by previous interventions on non-bariatric individuals with OSA that have been completed successfully and safely (Kline *et al.*, 2011; Sengul *et al.*, 2011) and exercise interventions/guidelines relating to bariatric populations (Pouwels *et al.*, 2015, King and Bond, 2013). In chapter seven, patients were only asked if they would be willing to complete two training sessions per week (and were willing to do this) and about interval-based exercise. However, the frequency of training has been increased in the current intervention (to three sessions per week) and the protocol based on

continuous moderate-intensity aerobic work as these prescriptions were found to be more in-line with the research used to inform the programme design.

Patients in the exercise group will receive routine clinical care and also perform supervised moderate-intensity aerobic exercise and resistance training three times per week for the 12-week period leading up to weight-loss surgery. Each session will last approximately 60-70 minutes (warm-up, 30 minutes moderate-intensity aerobic work, 20 minutes resistance training, cool-down). The exercise modalities (cycling on a stationary bike or walking on a treadmill) chosen provide low-impact options for a population group who may be limited by comorbidities (Guh *et al.*, 2009). Light resistance training (upper body, lower body and trunk) with dumbbells and bands will be completed in mini-circuit formats.

Exercise intensity will be prescribed using information from each patient's CPET, which is considered to be the 'gold standard' test for evaluating exercise capacity (Stroescu *et al.*, 2012). CPET brings a high level of objectivity in exercise tolerance evaluation and provides information on multiple physiological parameters, which are needed for accurate and individualised exercise prescription (Stroescu *et al.*, 2012). Exercise intensity during the intervention will be monitored using heart rate domains and ratings of perceived exertion (RPE) – measured using Borg's CR-10 scale (Borg, 1982). RPE has been shown to be an acceptably reliable and valid marker of exercise intensity in obese people (Jakicic *et al.*, 1995).

Blood pressure will be checked at regular intervals (e.g. before training, post warm-up, post aerobic training). Exercise will be progressed gradually throughout the 12-weeks and longer warm-up and cool-down periods employed for safety. Two experienced exercise scientists will ensure treatment fidelity throughout the intervention. Patients will also receive one weekly individual face-to-face counselling session with a trained psychologist to support their exercise participation. These sessions will take place prior to and at the same location as the intervention. The usual care control will

follow routine clinical care throughout this period but will not take part in the exercise intervention.

8.2.5 Outcome measures

For this feasibility trial the emphasis will be focused primarily on the feasibility, acceptability and safety indicators:

1. Eligibility numbers: number of patients who meet the study inclusion criteria (number of patients per month over an 18-month period)
2. Recruitment figures: number of patients recruited to the study over time (number of patients per month over an 18-month period)
3. Exercise adherence: % of patients completing $\geq 75\%$ of exercise programme sessions
4. Retention figures: % of patients who have complete data collection
5. Clinicians acceptability of the trial: assessed in a researcher-led focus group at the hospital institution with 8-12 healthcare professionals responsible for the care of weight-loss surgery patients with OSA
6. Patient acceptability of the exercise intervention: previous PPI work (chapter seven) indicated a preference for study feedback to be given in a telephone interview with a member of the research team.
Therefore, researcher-led semi-structured telephone interviews will be conducted with all patients in the exercise group. Questions will focus on those identified as important regarding study feedback from the PPI work (how happy patients were with the exercise, whether they enjoyed the intervention, how they felt during and directly after the exercise session (and in the immediate longer term e.g. improved quality of life) and if the exercise caused them any pain or dizziness).
7. Study safety: number of adverse events directly related to the trial

The variability (standard deviations) of the following outcome measures will be examined to inform sample size planning for a subsequent definitive trial:

Primary Outcomes

- OSA Severity: Apnoea/hypopnoea index measurement using the Embletta portable diagnostic system, which has been validated against hospital-based polysomnography (Ng *et al.*, 2010). Patients will use this system at home.
- Daytime sleepiness: The Epworth Sleepiness Scale, which is a validated questionnaire for assessing daytime sleepiness (Johns, 1991; Johns, 1993).
- Cardiorespiratory fitness: The 6-Minute Walk Test has been reported to be a valid predictor of the anaerobic threshold (Sinclair *et al.*, 2012) and has been used previously to assess functional capacity in bariatric surgery patients (deSouza *et al.*, 2009). This simple field test is less resource intensive and more feasible to use than CPET for evaluation of cardiorespiratory fitness pre and post intervention (Stroescu *et al.*, 2012).

Secondary Outcomes

- Total daily physical activity levels: measured over a 7-day period using physical activity diaries and triaxial accelerometry at the hip (Actigraph GT3X). The PPI data collected in chapter seven indicated that these potential data collection tools might need to be further investigated once the sample is recruited.
- BMI
- Health-related quality of life: The EuroQoL EQ-5D, which has been previously validated in clinical settings (Jia and Lubetkin, 2005).
- Length of critical care and hospital stay

8.2.6 Baseline and post-intervention assessments

Written informed consent will be gained before any tests are conducted. Baseline assessments will then be conducted for both groups. Baseline assessment will include patient characteristics (age, sex and BMI) and examine daytime sleepiness (Epworth Sleepiness Scale), cardiorespiratory fitness (6-Minute Walk Test) and health-related quality of life (EuroQoL EQ-5D). Home-based polysomnography will also be conducted and patients will be asked to record their physical activity levels for the following week, reporting back to the researcher as instructed.

All patients will also conduct post-intervention assessments one week prior to surgery. Assessments will be conducted at the academic institution and follow the safety procedures identified in section 8.4. Researchers blinded to group allocation will collect baseline and post-intervention assessment data. A clinical member of the research team will obtain length of critical care and hospital stay from patient records following discharge.

8.2.7 Data analysis

The study statistician will conduct the statistical analysis in a blinded manner. Data analysis will be on the basis of intention to treat. The standard deviation of the changes in the outcome measures will be quantified along with 95% confidence intervals. The effect of exercise training on the outcomes will be analysed using a general linear model, including group as a fixed factor and baseline measures as a covariate. As this is a feasibility study and not concerned with effect size, no further evaluation of the outcome measures will be conducted (NIHR, 2016). The qualitative data from focus groups with healthcare professionals and telephone interviews with patients will be recorded, transcribed verbatim and analysed using thematic analysis (Gratton and Jones, 2004). Data management will abide by the governance guidelines of the two study institutions. The trial will be reported using the CONSORT guidelines as extended for the reporting of randomised pilot and feasibility trials (Eldridge *et al.*, 2016).

8.3 Criteria for Success

A subsequent definitive RCT will be viewed as feasible if the following criteria are met:

1. $\geq 80\%$ of patients have complete data collection
2. $\geq 80\%$ of patients achieve the adherence criteria (i.e. complete $\geq 75\%$ of exercise sessions)
3. There are no major concerns identified regarding acceptance of the intervention by patients and clinicians
4. The primary outcome measures have been confirmed and the associated standard deviations quantified for powering a definitive trial
5. The monthly eligibility and recruitment figures suggest that it is feasible to plan an adequately powered definitive trial with a realistic recruitment timeframe
6. Measurement methods for all outcomes have been confirmed
7. There are no adverse events directly linked to the trial

8.4 Research governance and monitoring

Approval for the study will be gained from the school ethics committee at the academic institution and the NHS Research and Development Office at the clinical site. NHS Research Ethics Committee and Health Research Authority (HRA) approvals will then be obtained. No study activity will commence until all approvals are completed. Study conduct will adhere to the Declaration of Helsinki (World Medical Association, 2013) and principles outlined in the UK Policy Framework for Health and Social Care Research (HRA, 2017). Where relevant, NHS research passports will be gained prior to the start of any research.

Two groups will manage the study, a research management group and a steering group. The research management group will receive weekly updates from the research team and meet monthly to discuss study progress/highlight any problems. The steering group will be led by an academic independent of

the two study institutions and will receive monthly updates from the research management group. This group will meet once every three months to ensure that the study is adhering to all guidelines and protocols and identify any areas of concern.

All adverse events will be recorded with both the research management and steering groups informed. Reporting will follow the HRA (2018) safety reporting guidelines. Adverse events will be detailed in all study documents and publications. All exercise testing and prescription will follow ACSM guidelines (Thompson *et al.*, 2007). The following control measures will also be implemented to reduce the risk of adverse events:

- Thorough pre-participation screening
- Exclusion of high-risk patients
- Exercise sessions supervised by experienced research nurses/exercise scientists trained in immediate/advanced life support
- Exercise sessions performed in the afternoon given the higher frequency of cardiovascular events during the early morning hours
- Prompt evaluation of prodromal symptoms
- Longer warm-up and cool-down periods
- Resuscitation equipment and oxygen immediately available
- Exercise termination if a patient experiences chest, back or abdominal pain, dizziness or an increase in systolic blood pressure to >180 mm Hg

Participants requiring further assessment will be transferred to the accident and emergency unit at the local clinical institution by a member of the research team or an ambulance if it is a medical emergency. The clinical institution will be informed of the study training and testing times and dates.

8.5 Patient and public involvement

The patient and public involvement (PPI) work conducted in chapter seven has provided invaluable information to inform the development of this protocol. PPI work will continue to inform the study to ensure that all work is acceptable and receives input from a patient perspective (patient representatives included in the research management and steering groups). All PPI work will follow INVOLVE (2012) guidance.

8.6 Dissemination

1. Academic dissemination: The feasibility study will be published in a high impact journal. The findings will also be presented at international and national conferences e.g. the annual congress of The Association of Anaesthetists of Great Britain and Ireland (AAGBI).
2. Patient-centred dissemination: Seminars/events pertaining to the research will be held at the two participating institutions for patients and relevant healthcare professionals to attend.
3. Public dissemination: A news item pertaining to the research will be written and sent to relevant organisations and groups (e.g. British Lung Foundation).

Chapter Nine: Overview and conclusions to this thesis

9.1 Overview of the findings: the diagnosis of OSA

It has been reported that a substantial number of people with OSA, even those with obesity, remain formally undiagnosed (Rejon-Parrilla, Garau, and Sussex, 2014; Chung, Abdullah and Liao, 2016). Therefore, one of the aims of this thesis was to examine how the relationship between physical activity and SDB could be used to improve OSA screening. In chapter four, it was found that a simple 'yes/no' question pertaining to self-reported slow-walking speed was independently associated with SDB outcomes in the large population-based dataset from the MESA. It was also reported that this easily answered question had a good response rate (98%) and compared favourably with other items present on existing OSA screening tools such as the STOP-Bang.

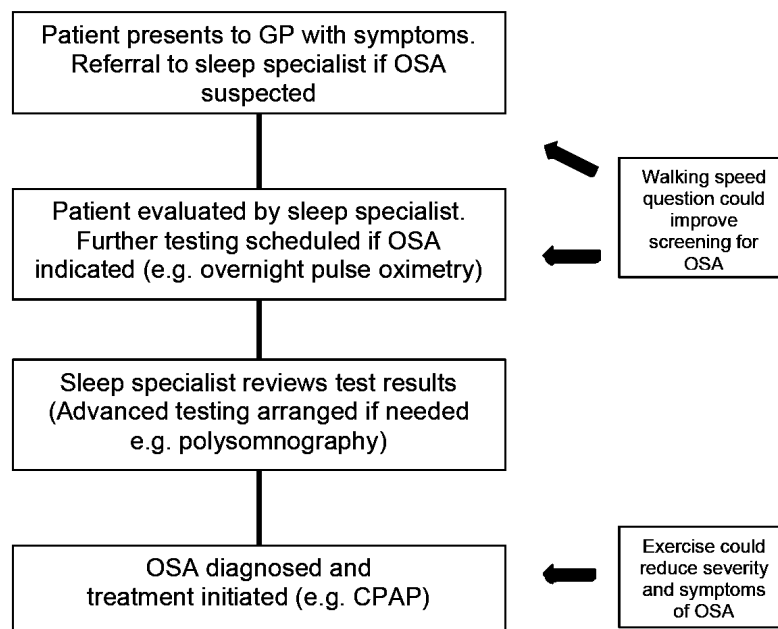


Figure 9.1: Clinical pathway for diagnosing and treating OSA in adults

Early detection of disease is an important component of current health care policy (Public Health England (PHE), 2016). At present, patients usually present to their general practitioner (GP) with signs of OSA such as excessive daytime sleepiness or very loud snoring (NHS, 2016). If OSA is suspected, the patient will be referred to a sleep specialist who will evaluate them for the disorder and determine if further testing is needed (NHS, 2016). These initial evaluation processes are based on patient history, clinical examination and screening questionnaires such as the STOP-Bang (British Lung Foundation, 2012; NHS, 2016). Figure 9.1 shows the current clinical care pathway for diagnosing and treating OSA in adults in the UK. The initial results from the thesis indicate that a patient's walking speed may help to identify whether they are likely to have OSA. Improving screening with a quick and simple walking speed question could have great benefits for OSA sufferers, as it would increase their chance of being identified and triaged for further testing and ultimately treatment to improve their health and quality of life. Without being identified, a person would continue to struggle with the disorder and its consequences and spend more time trying to find an answer for highly debilitating symptoms. This would impact negatively on the economy, especially the NHS with regards to the significant vascular comorbidities associated with untreated OSA (e.g. myocardial infarction, stroke) (Rejon-Parrilla, Garau and Sussex, 2014; Dawson, Singh and Chung, 2016). Further work is needed, but these preliminary findings suggest that clinicians should consider walking speed during their patient evaluation.

In chapter six, the findings from chapter four were progressed into a clinical context with weight-loss surgery patients, a group with a high prevalence of OSA (Chung, Abdullah and Liao, 2016). Efficient diagnosis and treatment of OSA is particularly important in these patients to reduce the risk of perioperative OSA-related complications (Riad and Chung, 2013). The work in this chapter examined whether replacing the BMI item in the STOP-Bang questionnaire, which is usually positive for all members of this population group, with a slow-walking speed item could improve its screening utility.

When the slow-walking speed item was added to this new model (STOPANG), it improved the area under the ROC curve from 0.64 to 0.70. Slow-walking speed was also found to be a more important factor than several other existing items on the STOP-Bang tool such as snoring, daytime sleepiness and hypertension.

In the current clinical pathway, all patients referred to bariatric and SWMS clinics at JCUH complete the STOP-Bang screening tool located on the referral form during their first clinical evaluation with a bariatric nurse specialist. Figure 9.2 shows the clinical care pathway for this patient group. The key findings from the current work suggest that a question pertaining to slow-walking speed could help to identify more patients with a high likelihood of OSA before they undergo weight-loss surgery. Identification prior to surgery could ultimately reduce the number of patients at risk of OSA-related surgical complications and the added trauma that these may involve (Riad and Chung, 2013; Chung, Abdullah and Liao, 2016). As discussed in chapter six, improved screening with a slow-walking speed question would also be advantageous for the clinical care team, as they would be more prepared for surgeries (e.g. have appropriate perioperative management plans in place such as increased patient monitoring and caution when using opioids as they can worsen OSA) (Danjoux and Habgood, 2016; Dawson, Singh and Chung, 2016). Therefore, the results from this thesis could ultimately lead to a safer and more efficient clinical care pathway for weight-loss surgery patients with OSA. Further research is most definitely warranted to examine these preliminary findings.

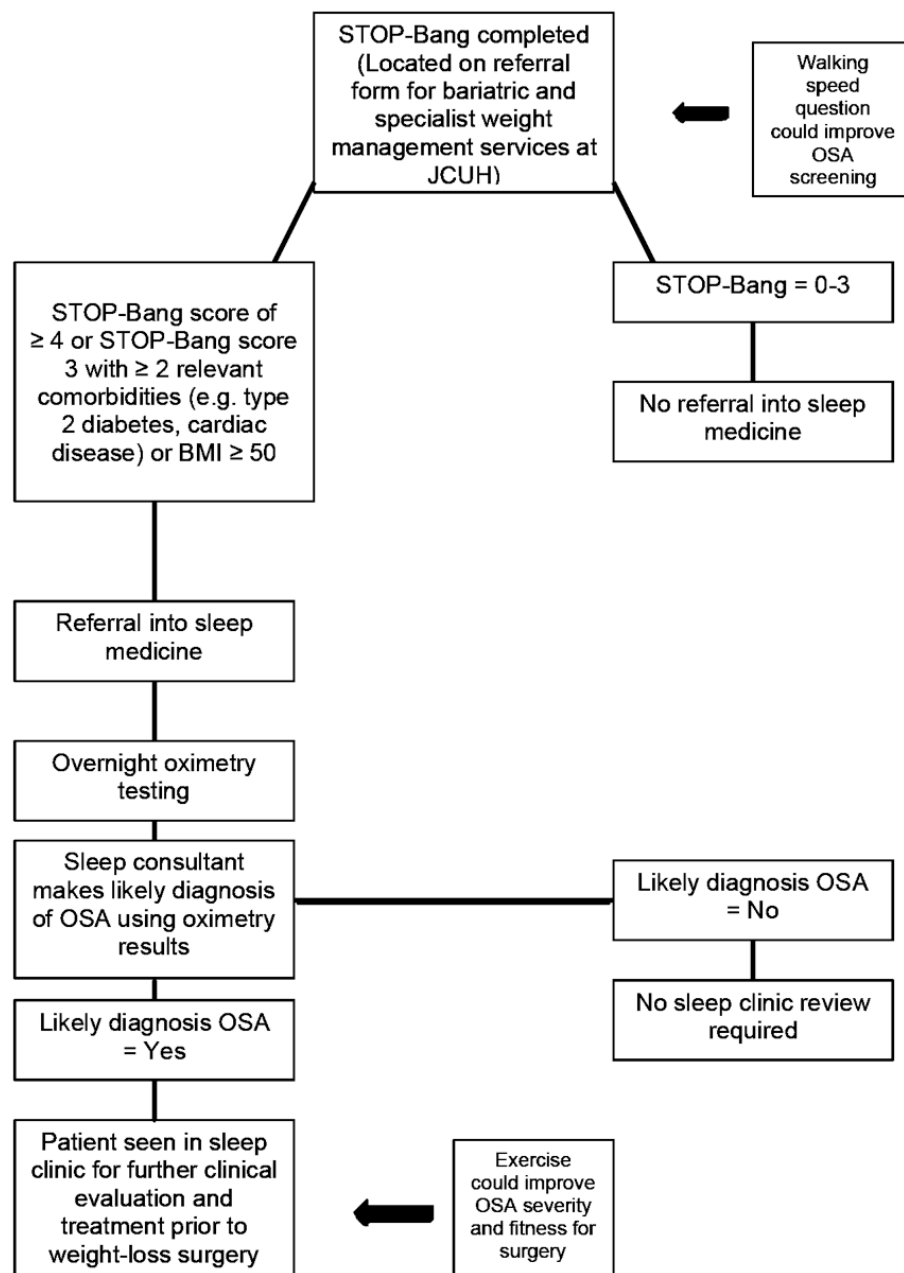


Figure 9.2: Clinical pathway for identifying and treating OSA in bariatric and specialist weight management patients prior to weight-loss surgery at JCUH

9.2 Overview of the findings: the treatment of OSA

Poor adherence to CPAP, the 'gold-standard' treatment for OSA, and incomplete efficacy of secondary therapies (e.g. MADs, weight loss) pointed to the need for alternative management strategies for this debilitating disorder (NICE, 2008). The beneficial impact of exercise on OSA was recognised as a potential solution to the problem, yet further work to expand the evidence base regarding the effects of exercise on the severity and symptoms of OSA had been called for (Iftikhar *et al.*, 2017). Therefore, the treatment pathway in the thesis aimed to consolidate the existing body of knowledge on this topic (conducting an overview of reviews on the effects of exercise on OSA) and undertake important preparatory work (examining a potential outcome measure and conducting PPI work) towards the design of a high-quality RCT to advance the research body.

Firstly, the critical overview of reviews provided evidence to suggest that in adults with OSA (on average reviews reported data on generally healthy males and females who were >40 years old with AHI >15 events/h and BMI >25 kg/m²), exercise has a significant and potentially clinically meaningful effect on reducing OSA severity and daytime sleepiness, independent of BMI. From this chapter, it was concluded that currently, despite some variability between reviews regarding the size of effect (AHI reductions between 4.66 and 17.23 events/h were reported in RCT-only meta-analyses), there is a robust research body supporting the use of exercise as an "adjunctive therapy" option for the management of OSA (Iftikhar *et al.*, 2017. p. 12).

These results are highly encouraging and indicate that exercise may be another strategy to help treat this disorder (Figure 9.1). Therefore, clinicians should ensure that the benefits of exercise for improving OSA are explained and highlighted to patients and encourage them to incorporate exercise into their management programmes. Exercise may be welcomed by many patients struggling with current therapy options, especially as the amount of

exercise needed to see beneficial effects is not excessive and even less than the physical activity guidelines for adults (NHS, 2018). Reviews in chapter three indicated a trend towards regimens that were conducted three times per week and included ≥ 30 minutes moderate intensity aerobic exercise + resistance training (Araghi *et al.*, 2013; Iftikhar, Kline and Youngstedt, 2014; Aiello *et al.*, 2016; Iftikhar *et al.*, 2017). For example, if a patient was using CPAP but struggling to adhere to it and therefore not getting optimal benefits, the addition of exercise to their management plan could make up for any shortfalls in their CPAP usage and keep their OSA in a lower severity category. Likewise, if a patient had a milder form of the disorder and could not use MADs, exercise may be able to bring their OSA to a manageable level. Also, unlike CPAP and MADs, the side effects of exercise are more positive e.g. exercise may lead to improvements in cardiorespiratory fitness (Iftikhar, Kline and Youngstedt, 2014).

In particular, it is promising that the preliminary evidence indicates that exercise could provide patients with an effective strategy to deal with excessive daytime sleepiness, which may not be addressed as well with other treatment options (Bratton *et al.*, 2015; Iftikhar *et al.*, 2017). Improved management of this functionally limiting symptom would enable patients to be more effective in their everyday lives and safer when driving, increasing quality of life and work productivity and decreasing the number of OSA-related road traffic accidents (Rejon-Parrilla, Garau and Sussex, 2014). This could help the economy as it's estimated that the cost of one fatal road traffic accident can be as much as £1.5 million (British Lung Foundation, 2012).

As highlighted in figure 9.2, weight-loss surgery patients identified as having OSA are treated for the disorder prior to surgery as part of routine clinical care. Usual clinical care involves CPAP used 8-12 weeks preoperatively (NICE, 2008; Danjoux and Habgood, 2016). Although exercise had been shown to have benefits for treating OSA in adults, no studies had examined whether exercise in the preoperative period could help to improve this patient group's OSA and guidance for providing safe

and effective exercise prior to elective major surgery was limited (Iftikhar, Kline and Youngstedt, 2014; Iftikhar *et al.*, 2017; Tew *et al.*, 2018). The patient-informed protocol in this thesis provides the crucial early steps needed to initiate potential improvements to clinical care for this high-risk patient group (Dawson, Singh and Chung, 2016). Improving the preoperative stage of the clinical pathway by adding exercise alongside CPAP could enable patients to enter the perioperative period with greater physiological reserve and less severe OSA, reducing perioperative risk and potentially improving recovery and minimising the length of hospital stay (Dawson, Singh and Chung, 2016; Tew *et al.*, 2018). This would decrease the strain on the patient's support network and clinicians and reduce health care costs (Dawson, Singh and Chung, 2016). It would also place patients at a vantage point for furthering their weight loss post surgery, especially as they may have established a regular habit of exercise during the preoperative phase (Tew *et al.*, 2018). A brief overview of the protocol is provided in figure 9.3.

Aim: The aim of the trial is to assess the feasibility and acceptability of delivering an exercise intervention to patients with OSA who undergo weight-loss surgery in order to examine whether a full-scale trial is viable (NIHR, 2016).

Methods: Forty-two weight-loss surgery patients with clinically diagnosed moderate-to-severe OSA will be randomly allocated 2:1 to intervention (usual care and exercise) or usual care control (no exercise). The intervention group will perform 60-70 minutes of supervised, low-impact, moderate-intensity aerobic exercise and resistance training 3 times per week for the 12-week period leading up to surgery. Patients will also receive one weekly individual face-to-face counselling session with a trained psychologist to support their participation. Feasibility, acceptability and safety indicators will be assessed throughout an 18-month recruitment period, during the 12-week intervention and post patient discharge. Outcomes to be assessed prior to randomisation and one week prior to surgery include OSA severity, daytime sleepiness, cardiorespiratory fitness, quality of life and daily physical activity-levels. Length of critical care and hospital stay will be recorded at patient discharge. The standard deviation of the changes in the outcome measures will be quantified along with 95% confidence intervals to inform sample size planning for a definitive trial. Qualitative data will be analysed using thematic analysis. Criteria for success related to the above indicators and outcomes will be reviewed once all data is collected to determine whether a full definitive trial is warranted.

Ethics and Dissemination: NHS Research Ethics Committee and Health Research Authority approvals will be obtained for this work. Findings will be disseminated through academic journals and conferences, patient-centred seminars and relevant national health organisations.

Figure 9.3: The benefits of exercise for obese people with OSA who undergo weight-loss surgery: A protocol for a feasibility trial

A final point to note from the treatment pathway of this thesis is that pertaining to the work from chapter five regarding FMD%, a purported early indicator of atherosclerosis, which is reported to be reduced in people with OSA (Ali *et al.*, 2014). The results from this chapter indicate that people with OSA do not actually demonstrate a clinically important reduction in flow-mediated dilation when data is analysed using more appropriate allometric-based statistical methods (Atkinson *et al.*, 2016).

This finding indicated that FMD% was not suitable for use as an outcome measure in the protocol presented in chapter eight (FMD% was proposed to be the outcome measure pertaining to the cardiovascular consequences of OSA in this trial) and also highlighted that future researchers need to be cautious when interpreting the literature and analysing data regarding flow-mediated dilation in OSA patients.

9.3 Strengths and limitations of this thesis

There are a number of strengths to this thesis and also some limitations as highlighted within each chapter, the principal of which will now be discussed. To begin with, the work conducted in this thesis was novel and has the potential to advance the diagnostic and treatment pathways for OSA. The overview of reviews, which was conducted in a systematic and comprehensive manner, is the first of its kind to provide a detailed critique and examine the consistency and quality of current meta-analyses on the topic of exercise as a treatment for OSA. This comprehensive and clear document could improve the “uptake and application of knowledge” by busy health care professionals who may not have the time to collate and read multiple research papers (Pollock *et al.*, 2016, p. 2). This is also the first body of work to examine how physical activity could be used to improve the diagnosis of OSA, as no screening tools have, to date, included an item pertaining to a slow-walking speed. Another strength is that the datasets used for the analyses in chapters four and five were from a large, population-based, multi-ethnic study. The research in these chapters was adequately powered and can be generalised to people from different ethnic groups. Also, throughout the thesis great attention was taken to ensure that appropriate statistical techniques were employed for all data analyses, which increases confidence in the results obtained. Finally, all of the studies conducted as part of this thesis found a similar trend regarding the relationship between physical activity and OSA, which adds strength to the overall conclusions drawn from this work.

However, there are also limitations to the research presented, which need to be acknowledged. Firstly, in chapter three it was observed that there were a number of quality-related issues (e.g. reporting errors, publication bias) across the reviews, which need to be considered when examining the conclusions drawn from this work. Secondly, it is felt that the AMSTAR tool used to judge the methodological quality of the four reviews might not have provided the most appropriate assessment of all four papers. However, there was limited and conflicting guidance available regarding the optimal tool for use when assessing the quality of systematic reviews in the overview process (Pollock *et al.*, 2016). A further limitation of the thesis pertains to the work conducted in chapters four and five. As this research was based on cross-sectional data, one can only speculate about proposed causal mechanisms. Yet, the fact that the results support the predominant theme found within the thesis and the literature regarding the relationship between SDB and exercise does strengthen the inferences made in chapter four. A final limitation is that PSG was not used for SDB diagnosis in chapters four, five and six. In the MESA, SDB was self-reported on a questionnaire, and in the clinical work in chapter six, diagnosis of OSA was a likely diagnosis based on oximetry data from a relatively small sample of patients (N = 122). These principal limitations of the thesis need to be taken into account when making final evaluations of the evidence presented.

9.4 Overall conclusions to this thesis

This thesis has examined the role of physical activity in the diagnosis and treatment of OSA. Overall, there was a consistent message throughout supporting the independent relationship between increased physical activity and decreased OSA severity.

Concerning the diagnosis of OSA, the work presented in this thesis has the potential to improve public health by facilitating early detection of disease (PHE, 2016). The novel findings presented indicate that a simple, self-reported slow-walking speed question has the potential to:

- a) Improve screening for OSA in adults.
- b) Improve the diagnostic utility of the STOPANG tool in weight-loss surgery patients.

Effective management of OSA is essential for improving health and wellbeing and enabling people to fulfil meaningful roles within their families and wider society (PHE, 2016). The encouraging body of work presented in this thesis suggests that:

- a) There is a robust evidence-base supporting the use of exercise as an “adjunctive therapy” for treating the severity and symptoms of OSA in adults (Iftikhar *et al.*, 2017. p. 12).
- b) People with OSA do not demonstrate a clinically important reduction in flow-mediated dilation. Therefore, FMD% is not useful as an outcome measure in trials examining the effects of exercise on OSA.
- c) Weight-loss surgery patients with OSA are willing to take part in a supervised exercise-based RCT prior to surgery to improve their symptoms of OSA, quality of life and physical fitness.

Future research should:

- a) Examine whether a slow-walking speed question can improve the diagnostic utility of the STOP-Bang tool in the general adult population.
- b) Employ PSG and larger clinical sample sizes to further investigate whether the addition of a slow-walking speed question can improve the diagnostic utility of the STOPANG tool in weight-loss surgery patients.
- c) Focus on the conduct of high quality RCTs using larger and more diverse sample groups and longer research timeframes to advance the evidence base pertaining to the effects of exercise on OSA in adults.
- d) Progress the protocol for a feasibility RCT examining the benefits of exercise for obese people with OSA who undergo weight-loss surgery into the next research phase.

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Appendix One:

The STOP-Bang questionnaire (Chung *et al.*, 2008; Chung *et al.*, 2014)

STOP-Bang Questionnaire

1. **S**noring: Do you snore loudly (loud enough to be heard through closed doors)?
Yes No
2. **T**ired: Do you often feel tired, fatigued, or sleepy during daytime?
Yes No
3. **O**bserved: Has anyone observed you stop breathing during your sleep?
Yes No
4. **B**lood **P**ressure: Do you have or are you being treated for high blood pressure?
Yes No
5. **B**MI: BMI more than 35 kg/m²?
Yes No
6. **A**ge: Age over 50 years old?
Yes No
7. **N**eck circumference: Neck circumference greater than 40 cm?
Yes No
8. **G**ender: Male?
Yes No

Appendix Two:

The Epworth Sleepiness Scale (Johns, 1991; Johns, 1993)

THE EPWORTH SLEEPINESS SCALE

Name: _____

Today's date: _____ Your age (years): _____

Your sex (male = M; female = F): _____

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently try to work out how they would have affected you. Use the following scale to choose the *most appropriate number* for each situation:

- 0 = would *never* doze
- 1 = *slight* chance of dozing
- 2 = *moderate* change of dozing
- 3 = *high* chance of dozing

Situation	Chance of dozing
Sitting and reading	_____
Watching TV	_____
Sitting, inactive in a public place (e.g. a theater or a meeting)	_____
As a passenger in a car for an hour without a break	_____
Lying down to rest in the afternoon when circumstances permit	_____
Sitting and talking to someone	_____
Sitting quietly after a lunch without alcohol	_____
In a car, while stopped for a few minutes in the traffic	_____

Thank you for your cooperation

Appendix Three: PROSPERO Registration

PROSPERO
International prospective register of systematic reviews



UNIVERSITY of York
Centre for Reviews and Dissemination

Systematic review

1. * Review title.

Give the working title of the review, for example the one used for obtaining funding. Ideally the title should state succinctly the interventions or exposures being reviewed and the associated health or social problems. Where appropriate, the title should use the PI(E)COS structure to contain information on the Participants, Intervention (or Exposure) and Comparison groups, the Outcomes to be measured and Study designs to be included.

A critical overview of reviews on the effects of exercise on symptoms of obstructive sleep apnoea

2. Original language title.

For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

3. * Anticipated or actual start date.

Give the date when the systematic review commenced, or is expected to commence.
14/10/2013

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.
30/04/2019

5. * Stage of review at time of this submission.

Indicate the stage of progress of the review by ticking the relevant Started and Completed boxes. Additional information may be added in the free text box provided.

Please note: Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. Should evidence of incorrect status and/or completion date being supplied at the time of submission come to light, the content of the PROSPERO record will be removed leaving only the title and named contact details and a statement that inaccuracies in the stage of the review date had been identified.

This field should be updated when any amendments are made to a published record and on completion and publication of the review. If this field was pre-populated from the initial screening questions then you are not able to edit it until the record is published.

The review has not yet started: No

Review stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Provide any other relevant information about the stage of the review here (e.g. Funded proposal, protocol not yet finalised).

This systematic review is a component of S. Suri's PhD programme

This systematic review is a component of S. Suri's PhD programme

6. * Named contact.

The named contact acts as the guarantor for the accuracy of the information presented in the register record.

Greg Atkinson

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

Greg

7. * Named contact email.

Give the electronic mail address of the named contact.

greg.atkinson@tees.ac.uk

8. Named contact address

Give the full postal address for the named contact.

Health and Social Care Institute

Teesside University

Parkside West

Middlesbrough

TS1 3BA

UK

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

+44 (0)1642 342758

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be

completed as 'None' if the review is not affiliated to any organisation.

None

Organisation web address:

11. * Review team members and their organisational affiliations.

Give the title, first name, last name and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong.

Professor Greg Atkinson. Teesside University
Professor Alan Batterham. Teesside University
Professor Gerard Danjoux. James Cook University Hospital
Ms Sophie Suri. Teesside University
Mrs Janet Atkinson. Teesside University

12. * Funding sources/sponsors.

Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Include any unique identification numbers assigned to the review by the individuals or bodies listed.

This review is a component of Sophie Suri's PhD programme, which is funded by Teesside University.

13. * Conflicts of interest.

List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.

None

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members.

15. * Review question.

State the question(s) to be addressed by the review, clearly and precisely. Review questions may be specific or broad. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using P(I)E(C)OS where relevant.

Are exercise interventions effective for reducing symptoms of obstructive sleep apnoea (OSAS) in adults?

Which exercise are associated with the greatest improvements in the apnoea-hypopnoea index (AHI) and daytime sleepiness in adult OSAS patients?

Are the improvements in the AHI and/or daytime sleepiness independent from any intervention-mediated weight loss?

16. * Searches.

Give details of the sources to be searched, search dates (from and to), and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.

An appropriate search strategy will be formulated with the assistance of an information specialist, who will then search through the following databases: Applied Social Sciences Index and Abstracts (ASSIA),

Campbell Collaboration, Centre for Review and Dissemination, Database of Promoting Health Effectiveness Reviews (DoPHER), Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews, Cochrane Methodology Register, Database of Abstracts of Reviews or Effects (DARE), EMBASE, NHS Economic Evaluation Database (NHS EED), PROSPERO, PubMed, PsycINFO MEDLINE (Ovid), Sports Discus, SCOPUS and CINAHL. Searches will be limited to systematic reviews published from 1980 to present. No language restriction will be applied during the searches.

17. URL to search strategy.

Give a link to a published pdf/word document detailing either the search strategy or an example of a search strategy for a specific database if available (including the keywords that will be used in the search strategies), or upload your search strategy. Do NOT provide links to your search results.

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Do not make this file publicly available until the review is complete

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.

The prevalence of obstructive sleep apnoea (OSA) is increasing worldwide. The condition is characterised by frequent (sometimes 30 per hour) episodes of upper airway collapse during sleep. These episodes are measured as the primary outcome called the apnoea-hypopnoea index (AHI). The AHI is an independent risk factor for hypertension, stroke, cardiac arrhythmias and heart failure. A large AHI is related to other symptoms, such as severe sleepiness and fatigue during the day, thus reducing quality of life. These symptoms of obstructive sleep apnoea syndrome (OSAS) also increase the probability of diabetes, cognitive dysfunction, long-term sick leave and the risk of motor vehicle accidents.

19. * Participants/population.

Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.

Inclusion criteria

Adults (18 years and over) diagnosed as having obstructive sleep apnoea and/or obstructive sleep apnoea syndrome.

Exclusion criteria

Children (under 18), No other diagnosed sleep conditions such as central sleep apnoea.

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the nature of the interventions or the exposures to be reviewed.

Purposeful exercise interventions.

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

Any comparator.

22. * Types of study to be included.

Give details of the types of study (study designs) eligible for inclusion in the review. If there are no restrictions on the types of study design eligible for inclusion, or certain study types are excluded, this should be stated. The preferred format includes details of both inclusion and exclusion criteria.

Systematic reviews and/or meta-analyses on RCTs, observational studies, case-controlled or other quasi-experimental studies. Systematic reviews on diagnosis issues will be excluded.

23. Context.

Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.

Only studies from 1980 to present will be reviewed. No reviews on diagnosis issues.

24. * Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

The AHI measured pre- and post-intervention (with any follow-up period considered).

Timing and effect measures

25. * Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state 'None' or 'Not applicable' as appropriate to the review

Body mass Index (BMI),

The Oxygen Desaturation Index (ODI),

Daytime sleepiness, e.g., Epworth

Quality of life

Both outcomes measured pre- and post-intervention (any follow-up period considered).

Timing and effect measures

26. * Data extraction (selection and coding).

Give the procedure for selecting studies for the review and extracting data, including the number of researchers involved and how discrepancies will be resolved. List the data to be extracted.

At least two researchers will independently assess the eligible reviews. Disagreements about the eligibility of a particular review will be resolved by a third reviewer. Full papers will be obtained for eligible articles and

reviewed by two independent researchers and, if necessary, by a third reviewer.

27. * Risk of bias (quality) assessment.

State whether and how risk of bias will be assessed (including the number of researchers involved and how discrepancies will be resolved), how the quality of individual studies will be assessed, and whether and how this will influence the planned synthesis.

Quality appraisal will be completed using a modified version of the AMSTAR1 guidance.

28. * Strategy for data synthesis.

Give the planned general approach to synthesis, e.g. whether aggregate or individual participant data will be used and whether a quantitative or narrative (descriptive) synthesis is planned. It is acceptable to state that a quantitative synthesis will be used if the included studies are sufficiently homogenous.

A narrative synthesis is planned with a quantitative description of each systematic reviews pooled effect sizes (no further meta-analysis).

29. * Analysis of subgroups or subsets.

Give details of any plans for the separate presentation, exploration or analysis of different types of participants (e.g. by age, disease status, ethnicity, socioeconomic status, presence or absence or co-morbidities); different types of intervention (e.g. drug dose, presence or absence of particular components of intervention); different settings (e.g. country, acute or primary care sector, professional or family care); or different types of study (e.g. randomised or non-randomised).

None.

30. * Type and method of review.

Select the type of review and the review method from the lists below. Select the health area(s) of interest for your review.

Type of review

Cost effectiveness
No

Diagnostic
No

Epidemiologic
No

Individual patient data (IPD) meta-analysis
No

Intervention
Yes

Meta-analysis
No

Methodology
No

Narrative synthesis
Yes

Network meta-analysis
No

Pre-clinical
No

Prevention

PROSPERO
International prospective register of systematic reviews

No
Prognostic
No
Prospective meta-analysis (PMA)
No
Review of reviews
No
Service delivery
No
Synthesis of qualitative studies
No
Systematic review
Yes
Other
No

Health area of the review

Alcohol/substance misuse/abuse
No
Blood and immune system
No
Cancer
No
Cardiovascular
No
Care of the elderly
No
Child health
No
Complementary therapies
No
Crime and justice
No
Dental
No
Digestive system
No
Ear, nose and throat
No
Education
No
Endocrine and metabolic disorders
No
Eye disorders
No
General interest
No
Genetics
No
Health inequalities/health equity
No
Infections and infestations
No
International development

No
Mental health and behavioural conditions
No
Musculoskeletal
No
Neurological
No
Nursing
No
Obstetrics and gynaecology
No
Oral health
No
Palliative care
No
Perioperative care
No
Physiotherapy
No
Pregnancy and childbirth
No
Public health (including social determinants of health)
No
Rehabilitation
No
Respiratory disorders
Yes
Service delivery
No
Skin disorders
No
Social care
No
Surgery
No
Tropical Medicine
No
Urological
No
Wounds, injuries and accidents
No
Violence and abuse
No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.
English

There is an English language summary.

32. Country.

Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved.
England

33. Other registration details.

Give the name of any organisation where the systematic review title or protocol is registered (such as with The Campbell Collaboration, or The Joanna Briggs Institute) together with any unique identification number assigned. (N.B. Registration details for Cochrane protocols will be automatically entered). If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

None

34. Reference and/or URL for published protocol.

Give the citation and link for the published protocol, if there is one

Give the link to the published protocol.

Alternatively, upload your published protocol to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

No I do not make this file publicly available until the review is complete

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

Give brief details of plans for communicating essential messages from the review to the appropriate audiences.

We will submit the resulting manuscript to a leading journal in this field. In addition, we plan to disseminate the findings of this study to clinicians at James Cook University Hospital and within Fuse – The Centre for Translational Research in Public Health. The review will also be disseminated as part of S.Suri's PhD thesis.

Do you intend to publish the review on completion?

Yes

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords will help users find the review in the Register (the words do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

Sleep Apnoea, Obstructive

Exercise

Obesity

Systematic Review

Meta-analysis

Weight loss

37. Details of any existing review of the same topic by the same authors.

Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

38. * Current review status.

Review status should be updated when the review is completed and when it is published. For

PROSPERO
International prospective register of systematic reviews

newregistrations the review must be Ongoing.
Please provide anticipated publication date

Review_Completed_not_published

39. Any additional information.

Provide any other information the review team feel is relevant to the registration of the review.

40. Details of final report/publication(s).

This field should be left empty until details of the completed review are available.

Give the link to the published review.

Appendix Four:

SEARCH STRATEGY FOR CHAPTER THREE: A CRITICAL OVERVIEW OF REVIEWS ON THE EFFECTS OF EXERCISE ON THE SEVERITY OF OSA

OBSTRUCTIVE SLEEP APNOEA

“Sleep apnoea”

OR

“Sleep apnea”

OR

“Sleep-disorder*”

AND

EXERCISE

Exercise

OR

Exercis*

OR

Lifestyle

AND

REVIEW

Review

OR

Overview

OR

Meta*

Appendix Five:

AMSTAR tool (Shea *et al.*, 2007)

AMSTAR – a measurement tool to assess the methodological quality of systematic reviews.

1. Was an 'a priori' design provided?

The research question and inclusion criteria should be established before the conduct of the review.

- ☐ Yes
- ☐ No
- ☐ Can't answer
- ☐ Not applicable

Note: Need to refer to a protocol, ethics approval, or pre-determined/a priori published research objectives to score a "yes."

2. Was there duplicate study selection and data extraction?

There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.

- ☐ Yes
- ☐ No
- ☐ Can't answer
- ☐ Not applicable

Note: 2 people do study selection, 2 people do data extraction, consensus process or one person checks the other's work.

3. Was a comprehensive literature search performed?

At least two electronic sources should be searched. The report must include years and databases used (e.g., Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.

- ☐ Yes
- ☐ No
- ☐ Can't answer
- ☐ Not applicable

Note: If at least 2 sources + one supplementary strategy used, select "yes" (Cochrane register/Central counts as 2 sources; a grey literature search counts as supplementary).

4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?

The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.

- ☐ Yes
- ☐ No
- ☐ Can't answer
- ☐ Not applicable

Note: If review indicates that there was a search for "grey literature" or "unpublished literature," indicate "yes." SIGLE database, dissertations, conference proceedings, and trial registries are all considered grey for this purpose. If searching a source that contains both grey and non-grey, must specify that they were searching for grey/unpublished lit.

5. Was a list of studies (included and excluded) provided?

A list of included and excluded studies should be provided.

- ☐ Yes
- ☐ No
- ☐ Can't answer
- ☐ Not applicable

Note: Acceptable if the excluded studies are referenced. If there is an electronic link to the list but the link is dead, select "no."

6. Were the characteristics of the included studies provided?

In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g., age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.

- ☐ Yes
- ☐ No
- ☐ Can't answer
- ☐ Not applicable

Note: Acceptable if not in table format as long as they are described as above.

7. Was the scientific quality of the included studies assessed and documented?

'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.

- ☐ Yes
- ☐ No
- ☐ Can't answer
- ☐ Not applicable

Note: Can include use of a quality scoring tool or checklist, e.g., Jadad scale, risk of bias, sensitivity analysis, etc., or a description of quality items, with some kind of result for EACH study ("low" or "high" is fine, as long as it is clear which studies scored "low" and which scored "high"; a summary score/range for all studies is not acceptable).

8. Was the scientific quality of the included studies used appropriately in formulating conclusions?

The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.

- ☐ Yes
- ☐ No
- ☐ Can't answer
- ☐ Not applicable

Note: Might say something such as "the results should be interpreted with caution due to poor quality of included studies." Cannot score "yes" for this question if scored "no" for question 7.

9. Were the methods used to combine the findings of studies appropriate?

For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e., Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e., is it sensible to combine?).

- ☐ Yes
- ☐ No
- ☐ Can't answer
- ☐ Not applicable

Note: Indicate "yes" if they mention or describe heterogeneity, i.e., if they explain that they cannot pool because of heterogeneity/variability between interventions.

10. Was the likelihood of publication bias assessed?

An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test, Hedges-Olken).

- ☐ Yes
- ☐ No
- ☐ Can't answer
- ☐ Not applicable

Note: If no test values or funnel plot included, score "no". Score "yes" if mentions that publication bias could not be assessed because there were fewer than 10 included studies.

11. Was the conflict of interest included?

Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.

- ☐ Yes
- ☐ No
- ☐ Can't answer
- ☐ Not applicable

Note: To get a "yes," must indicate source of funding or support for the systematic review AND for each of the included studies.

Shea et al. *BMC Medical Research Methodology* 2007 **7**:10 doi:10.1186/1471-2288-7-10

Additional notes (in italics) made by Michelle Weir, Julia Worswick, and Carolyn Wayne based on conversations with Bev Shea and/or Jeremy Grimshaw in June and October 2008 and July and September 2010.

Cross-sectional Association between Walking Pace and Sleep-disordered Breathing

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Key words

- obstructive sleep apnoea
- physical activity
- screening
- frailty

Abstract

Sleep-disordered breathing is an important comorbidity for several diseases, including stroke. Initial screening tools comprise simple yes/no questions about known risk factors for sleep-disordered breathing, e.g., obesity, sex. But walking speed has not been investigated in this context. We examined the cross-sectional association between walking pace and sleep-disordered breathing in the population-level Multi-Ethnic Study of Atherosclerosis. A sample of 2912 men and 3213 women (46–87 years) reported perceived walking pace outside their homes. A walking pace <0.89 m/s was deemed “slow”, with ≥0.89 m/s considered “average/brisk” according to validated thresholds. Sample prevalence

were: sleep apnoea (3.5%), self-reported apnoeas (8.4%), loud snoring (20.5%), daytime tiredness (22.2%) and slow-walking pace (26.9%). The 95% CI risk differences (multivariable-adjusted) for slow vs. faster walking pace were: sleep apnoea (0.4–2.5%), self-reported apnoeas (0.1–3.8%), loud snoring (1.2–8.3%), and daytime tiredness (3.0–7.8%). Risk differences were similar between sexes. The multivariable-adjusted risk ratio indicated that slower walkers had 1.5 (95% CI: 1.0 to 2.1) times the risk of sleep apnoea vs. faster walkers. In conclusion, a slower walking speed was associated with a greater prevalence of sleep-disordered breathing, independently from other common screening factors. Therefore, a simple walking speed question may help consolidate screening for this disorder.

accepted after revision
April 01, 2015

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DOI <http://dx.doi.org/10.1055/s-0035-1549856>
Published online:
June 19, 2015
Int J Sports Med 2015; 36:
843–847 © Georg Thieme
Verlag KG Stuttgart · New York
ISSN 0172-4622

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Introduction

Sleep-disordered breathing refers to a severity continuum ranging from loud snoring to physician-diagnosed obstructive sleep apnoea. Obstructive sleep apnoea is characterized by multiple losses of airway patency during sleep leading to hypoxia, hypercapnia, sleep fragmentation and increases in inspiratory efforts, all of which contribute to negative physiologic changes within the cardiovascular and pulmonary systems [1]. Obstructive sleep apnoea affects 4–9% of the adult population, but prevalence can be much higher (sometimes >60%) in patients with stroke, heart disease and hypertension [12]. Obstructive sleep apnoea can also lead to excessive daytime tiredness, which can compromise daily functioning, decrease workplace productivity and increase the risk of motor vehicle accidents [25]. This presence of daytime tiredness leads to a diagnosis of obstructive sleep apnoea syndrome. The prevalence of moderate-to-severe sleep-disordered breathing can be as high as 20% in commu-

nity-living adults [7]. Screening for sleep-disordered breathing is particularly important from both public health and economic perspectives [6]. It is also important to screen for sleep-disordered breathing in patients with other underlying conditions who require surgery [14]. Polysomnography is the gold standard diagnostic procedure for sleep-disordered breathing severity, yet is costly and generally only available in tertiary referral sleep centres [20]. Therefore, various screening tools have been designed for sleep-disordered breathing, such as “STOP-Bang”. This particular screening tool comprises 8 simple yes/no questions relating to risk factors (e.g., male sex, body mass index (BMI) >35 kg/m²) and indicators (e.g., snoring, daytime tiredness) for the disorder [5]. Some of these questions, e.g., loudness of snoring and occurrence of apnoea, are difficult to answer because they can rely on the presence of a bed partner. There are other diagnostic tools for sleep-disordered breathing including the Berlin Questionnaire and the 4-Variable Screening Tool [16]. No screening tool has, to date, included an item relating to physical activity.

Although the potential physiological mechanisms have not yet been fully elucidated (► Fig. 1), low levels of habitual physical activity are associated with worse severity of sleep-disordered breathing [10,17]. One indicator of physical activity, which is also a robust indicator of general frailty, is reported walking speed [22]. Health-related thresholds for low and high walking speeds have recently been formulated [4]. Therefore, we hypothesised that a simple yes/no question, similar to those in existing screening tools, but pertaining to reported walking speed, is associated with the severity of outcomes related to sleep-disordered breathing. We tested this hypothesis with the large population-based dataset from the multi-ethnic study of atherosclerosis (MESA).

Methods



Participants

The MESA is a large population-based study examining the early stages of cardiovascular disease. The research objectives and design have been published elsewhere [3]. The MESA study was approved by the local Institutional Review Boards of each participatory study site. Our cross-sectional analysis of the MESA dataset was approved by the local research ethics committee. This study also meets the ethical standards of the international Journal of Sports Medicine [9].

The MESA participants were 6814 men (47%) and women (53%) aged between 45–84 years from 6 communities in the US. Participants were from 4 different ethnic groups; white (39%), African-American (28%), Hispanic (22%), Chinese-American (12%). Data for the MESA were collected during 5 examination points over a 12-year period. Data for the present study were analysed from exam 2, undertaken between 2002 and 2004.

Measurement procedures

The outcomes relating to sleep-disordered breathing were physician-diagnosed sleep apnoea, self-reported apnoeic events, loud snoring heard behind a closed door and daytime tiredness. These outcomes were measured using a self-administered sleep questionnaire, as detailed previously by Yeboah et al. [27]. Participants could choose from a list of answers for each question with 'don't know' provided as a response for apnoea and snoring items. Guidelines from the American College of Physicians indicate that polysomnography has, and continues to be used routinely for the diagnosis of obstructive sleep apnoea [18]. It is reasonable therefore to assume that participants who answered 'yes' to the question relating to physician-diagnosed sleep apnoea had undergone polysomnography as part of their diagnostic pathway [21]. An interviewer-administered physical activity questionnaire was also completed. One question was: 'When you walk outside of your home, what is your usual pace?' 5 response options were provided from 'no walking at all' to 'brisk or striding'. Self-reported walking speed has been shown to be a good marker of measured walking speed in older adults in a recent large population-based study [24]. To facilitate a simple yes/no context in keeping with the traditional screening tools, a walking speed <0.89 m/s (or no reported walking) was classified as "slow", with ≥0.89 m/s classified as "average/brisk". The threshold used to define slow walking speed was informed by Stanaway et al. [22], who reported that walking slower than 0.89 m/s was predictive of mortality. The self-reporting of the relevant variables in the MESA is in the tradition of items on the

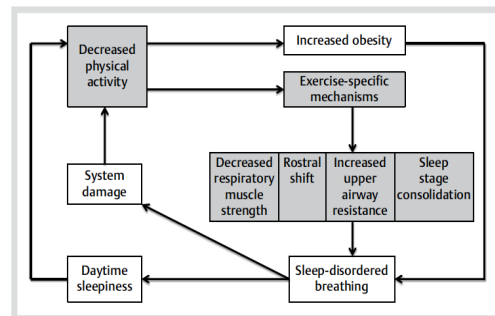


Fig. 1 The potential causal pathway(s) between physical activity and severity of sleep-disordered breathing.

current clinical STOP-Bang screening tool and facilitates a large sample of participants for data analysis. Our other study covariates included age, sex and ethnicity. Each participant's BMI and blood pressure were measured during clinical evaluation [3].

Data reduction

All outcome variables were dichotomised in keeping with current screening tools, such as the STOP-Bang. Responses to the 'how loud is your snoring?' question in MESA were recoded into whether snoring was "extremely loud- can be heard through a closed door" or not. Responses to 'how often do you feel excessively (overtly) sleepy during the day?' were recoded into never/sometimes and often/almost always. Other items, including physician-diagnosed sleep apnoea were already in a dichotomised format.

Statistical analysis

Data analysis was completed in the Statistical Package for the Social Sciences (SPSS, version 21) and Stata (StatCorp, Texas, version 12.1). Data were analysed with multivariable-adjusted binomial regression (with an identity link function), providing risk differences and their confidence intervals (95% CI). Analyses were adjusted for age, sex and ethnicity. Multivariable-adjusted Cox regression with a constant time-to-event variable [2] was employed to derive prevalence risk ratios and associated 95% CIs for the 6 STOP-Bang items, as well as for our additional slow walking speed question. We defined the minimum clinically important effect as a prevalence risk ratio of 1.11. This effect size implies that for every 10 people with sleep apnoea who have a slow walking speed there are 9 people with sleep apnoea who have a fast walking speed; that is, one in 10 sleep apnoea cases is associated with a slow walking speed. Thresholds for moderate, large, very large, and extremely large effects were deemed to be risk ratios of 1.43 (10/7), 2 (10/5), 3.3 (10/3), and 10 (10/1), respectively.

Results



Faster walkers were, on average, 3.5 years younger and 2.3 kg/m² lower in BMI than slower walkers. Faster walkers also comprised a lower proportion of women and African-American participants, and a higher proportion of white participants (► Table 1). The mean total number of medications was slightly (0.4) higher in slow walkers than in average/brisk walkers.

The prevalence of sleep-disordered breathing outcomes in the dataset is presented in **Table 2**. The prevalence of physician diagnosed sleep apnoea, self-reported apnoeas and loud snoring was higher in men compared with women (4.8 vs. 2.3%, 11.0 vs. 5.9% and 23.6 vs. 16.9% respectively). Slower walking speed was associated with an increased risk of all outcomes indicative of sleep-disordered breathing, including physician-diagnosed sleep apnoea (**Table 3**). These risk differences were adjusted for sex, age, and ethnic group. No substantial interactions were found between walking speed, ethnic group and sex. Risk differences were also similar when people who reported no walking at all were removed from the analyses. We investigated whether slow walking speed was an independent risk factor for physician-diagnosed sleep apnoea compared with other yes/no type outcomes present in traditional obstructive sleep apnoea screening tools. Questions relating to apnoea incidence, and loud snoring were, as expected, the strongest independent predictors of sleep apnoea (**Table 4**). Body mass index was also an independent predictor of sleep apnoea (prevalence risk ratio: 1.7). Nevertheless, the strength of the independent association of slow-walking speed was approaching that of BMI. People who walked relatively slowly had 1.5-times the risk of having sleep apnoea compared with people who walked at a faster pace. This prevalence risk ratio was higher than the point estimates of the prevalence risk ratios for the screening items of daytime tiredness, sex and hypertension (**Table 4**).

Table 1 Characteristics of the slow and average/brisk walkers at examination 2 in the MESA sample.

Characteristic	Slow walkers (n = 1 649)	Average/ brisk walkers (n = 4 476)	95 % CI for difference
Age (mean \pm SD years)	66.2 \pm 10.2	62.7 \pm 9.9	2.9 to 4.1
BMI (mean \pm SD kg/m ²)	30.0 \pm 6.2	27.7 \pm 5.0	2.0 to 2.6
Proportion women (%)	59%	50%	6% to 12%
Total no. of medications (mean \pm SD)	5.4 \pm 3.8	5.0 \pm 3.7	0.2 to 0.6
Ethnicity proportions (%)			
White	31%	43%	-9% to -15%
African-American	38%	23%	12% to 18%
Hispanic	22%	21%	-1% to 3%
Chinese-American	9%	13%	-2% to -6%

Table 2 The prevalence of sleep-disordered breathing outcomes in men, women and the overall MESA sample.

Sleep-disordered breathing outcome	Prevalence in men	Prevalence in women	Overall prevalence N (%)
Physician-diagnosed sleep apnoea	140/2 912 (4.8%)	73/3 213 (2.3%)	213/6 125 (3.5%)
Self-reported apnoeas	240/2 168 (11.0%)	138/2 335 (5.9%)	378/4 503 (8.4%)
Loud snoring	347/1 472 (23.6%)	204/1 207 (16.9%)	551/2 679 (20.5%)
Daytime tiredness	637/2 950 (21.6%)	740/3 245 (22.8%)	1 377/6 195 (22.2%)

The denominators vary for different outcomes depending on the number of 'don't know' responses to each STOP-Bang question

Table 3 Multivariable-adjusted risk differences between slow and average/brisk walkers for sleep-disordered breathing.

Study outcome	Risk ('slow' walking speed)	Risk ('average/brisk' walking speed)	Risk difference	95 % Confidence interval
Diagnosed sleep apnoea	4.7%	3.2%	1.5%	0.4% to 2.5%
Self-reported apnoeic events	10.7%	8.7%	2.0%	0.1% to 3.8%
Loud snoring	24.9%	20.1%	4.8%	1.2% to 8.3%
Daytime tiredness	26.4%	21.0%	5.4%	3.0% to 7.8%

Multivariable risk differences were similar across ethnic groups; for men and women; when people who reported no walking at all were removed from the analysis

Discussion

In this large population-based study, slow-walking speed was independently associated with an increased risk of sleep-disordered breathing outcomes. A simple yes/no question relating to slow walking speed compared favourably with other items present on existing screening tools for sleep-disordered breathing, including sex, daytime tiredness and hypertension.

The prevalence of diagnosed sleep apnoea was greater in men (4.8%) than in women (2.3%). Nevertheless, the multivariable-adjusted association between sex and sleep apnoea was weak and not statistically significant (**Table 4**), suggesting that sex-related covariates, such as BMI, might be more influential than sex *per se*. We also did not find a substantial interaction between sex and slow walking speed – sleep apnoea association. Endeshaw et al. [7] also analysed a population-level dataset (The Cardiovascular Health Study) and reported an association between slow-walking speed and sleep-disordered breathing, but only in women. The authors reported that this sex-specific finding was unexpected, but postulated that the protective effect of female hormones on airway collapse is lost after the menopause. Endeshaw et al. [7] obtained polysomnographic data from their participants while they slept at home, allowing the quantification of the rate of apnoeas and hypopnoeas, in contrast to the self-report approach employed in the present study. Nevertheless, the sample size in the current study was substantially larger than theirs (n=6 125 vs. 1 042), providing greater precision of estimation of effects in both sexes. In agreement with our findings, data from the Wisconsin Sleep Cohort Study indicated that the association between habitual exercise and sleep-disordered breathing was similar between men and women [17]. Ideally a large population-based study involving direct polysomnography is needed to clarify any sex differences in risk factors for sleep-disordered breathing.

The prevalence of the sleep-disordered breathing outcomes in the sample we analysed, including sleep apnoea, is consistent with those reported in other large studies [8,15,28]. Sleep apnoea can present itself as obstructive, central or 'mixed' (obstructive/central) in nature. Although the word 'obstructive' was not included in the sleep history questionnaire in the MESA, the prevalence of central and mixed sleep apnoea is much rarer in the general population than is obstructive sleep apnoea [26].

Table 4 Multivariable-adjusted prevalence risk ratios for the slow walking speed question and other yes/no questions traditionally included on screening tools such as the STOP-Bang tool.

STOP-Bang variable	Prevalence risk ratio	95 % Confidence interval
Stopping breathing during sleep	21.9	12.6 to 38.0
Loud snoring	2.1	1.5 to 3.1
BMI	1.7	1.2 to 2.5
Slow walking speed	1.5	1.0 to 2.1
Daytime tiredness	1.3	1.0 to 1.8
Sex	1.3	0.8 to 1.9
High blood pressure	1.2	0.9 to 1.7

Therefore, it is likely that the vast majority of cases of diagnosed sleep apnoea in the present study are obstructive in nature. The present study findings support the hypothesis that low levels of physical activity increase the severity of sleep-disordered breathing. One possible causal pathway for this hypothesis involves a bidirectional influence of obesity (► Fig. 1). A habitual slow walking pace may, over time, contribute to weight gain, which is an independent risk factor for sleep-disordered breathing [20]. Conversely, it is possible that more severe sleep-disordered breathing mediates more daytime sleepiness and, therefore, a decreased willingness or propensity for a faster walking pace. This pathway is supported by population-based research, which has found a statistically significant association between tiredness and a decreased walking speed [23]. Because BMI is on this potential causal pathway, we did not adjust for it in our primary analysis of risk differences. Nevertheless, in our secondary analysis, slow walking pace was compared against other items, including BMI, on popular screening tools for sleep-disordered breathing. Slow walking pace was found to be independently associated with the prevalence of diagnosed sleep apnoea, with a point estimate prevalence risk ratio that was slightly larger than those relating to sex, daytime tiredness and hypertension. This finding was consistent even if the participants who reported no walking at all were removed from the analysis. In terms of clinical relevance, the point estimate for the prevalence risk ratio for walking speed represents a moderate effect size, but the uncertainty (quantified by the 95 % CI) is such that the true population effect could be trivial (<1.11) to large (>2).

It is plausible that the causal pathway between walking speed and sleep-disordered breathing involves exercise-specific mechanisms, independent of BMI (► Fig. 1) [10,17]. It has been postulated that being physically active increases upper airway dilator muscle strength, reduces nasal resistance, improves sleep architecture and prevents lower-extremity fluid accumulation – the so called ‘Rostral Fluid Shift’ hypothesis [13]. All of these exercise-mediated changes may help to maintain airway patency during sleep and improve sleep-disordered breathing [11]. The rostral shift hypothesis has received considerable attention recently [13], and proposes that sedentary living leads to increased fluid accumulation in the legs during the daytime, which then shifts to the rostrum (towards the head) when lying supine for sleep. It is proposed that this fluid shift increases the propensity for upper airway collapse [19]. In the MESA, only 4205 people answered the question relating to loudness of snoring, with 1526 participants reporting ‘don’t know’. The response rate for self-reported perceptions of apnoea during sleep was also poor (► Table 2). In contrast, 6125 (98 %) of

the 6232 participants assessed at exam 2 were able to answer the walking speed question. Therefore, not only might the association between walking speed and sleep apnoea be stronger than other proposed risk factors, the question may be more easily-answered by participants than these other risk factors, e.g., daytime tiredness.

The large sample of our study, together with the fact that statistically significant associations were present, indicates acceptable statistical power. Nevertheless, a limitation of our study is that it was observational and cross-sectional in nature, with risk of temporal bias. Therefore, we can only speculate, as we have done above, about proposed causal mechanisms. However, our finding that walking speed (an indicator of physical activity and general frailty) is associated with less severe sleep-disordered breathing, independent from BMI, agrees with the results of recent randomised controlled trials of supervised exercise interventions [10].

In conclusion, we report an independent association between self-reported slow-walking speed and sleep-disordered breathing outcomes in a large population-based study. Prospective observational and experimental studies should follow to confirm these findings. We propose that a simple yes/no question relating to slow walking speed could improve the screening utility of the STOP-Bang questionnaire.

Acknowledgements

▼ This research was supported by contracts N01-HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168 and N01-HC-95169 from the National Heart, Lung, and Blood Institute and by grants UL1-TR-000040 and UL1-TR-001079 from NCI. The authors thank the other investigators, the staff, and the participants of the MESA study for their valuable contributions. A full list of participating MESA investigators and institutions can be found at <http://www.mesa-nhlbi.org>. The abstract for this paper was presented at the 19th annual congress of the European College of Sport Science in Amsterdam, July 2014 (Conference abstract ID: 265).

Conflict of interest: The authors have no conflict of interest to declare.

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Appendix Seven: Published journal paper



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Brachial artery diameter, but not flow-mediated dilation, is associated with sleep apnoea in the Multi-Ethnic Study of Atherosclerosis

Item type	Article
Authors	Atkinson, G. (Greg); Danjoux, G. R. (Gerard); Ells, L. J. (Louisa); Suri, S. (Sophie); Batterham, A. M. (Alan)
Citation	Atkinson, G., Danjoux, G., Ells, L. Suri, S., Batterham, A.M. (2016) "Brachial artery diameter, but not flow-mediated dilation, is associated with sleep apnoea in the Multi-Ethnic Study of Atherosclerosis" Journal of Hypertension; 34(3):410-3
DOI	10.1097/HJH.0000000000000808
Publisher	Lippincott, Williams & Wilkins
Journal	Journal of Hypertension
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Brachial artery diameter, but not flow-mediated dilation, is associated with sleep apnoea in the Multi-Ethnic Study of Atherosclerosis

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Running title: *Sleep apnoea and FMD%*

There was no financial support for any author of this study and no relationships with industry. G. Atkinson and AM Batterham gained access to the data and completed the statistical analysis. S. Suri assisted with literature searches and the writing of paper drafts. G. Danjoux and L. Ells commented on earlier drafts of the paper.

Total number of words: 2562

1 Figure

1 Table

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Abstract

The percentage flow-mediated dilation of the brachial artery (FMD%) is purported to be an early indicator of atherosclerosis and has been reported to be reduced in people with obstructive sleep apnoea. Nevertheless, FMD% scales poorly for, and is concomitantly dependent on, initial artery diameter, which may, itself, be higher in obstructive sleep apnoea patients. Therefore, for the first time, we aimed to quantify the differences in initial diameter and properly-scaled flow-mediated dilation between people with, and without, sleep apnoea. The prevalence of physician-diagnosed sleep apnoea, as well as initial and peak diameters of the brachial artery were recorded for 3354 participants in the Multi-Ethnic Study of Atherosclerosis (MESA). Arterial data were analysed using FMD% and an allometric approach, which scales the flow-mediated response properly for initial diameter. In the sex, race and age-adjusted model, initial diameter was 0.19 mm larger in sleep apnoea patients (95%CI: 0.07 to 0.32 mm, $P=0.003$) and correlated negatively with FMD% ($r= -0.43$, 95%CI: -0.57 to -0.26, $P<0.0005$). Using this same adjusted model, FMD% was $3.8\pm2.7\%$ for sleep apnoea patients ($n=104$) vs $4.4\pm2.7\%$ for undiagnosed people (95%CI for difference: -1.12 to -0.07%, $P=0.028$). Allometric scaling halved this FMD%-indicated sample difference in flow-mediated dilation (95%CI: -0.7% to 0.1%, $P=0.19$). In conclusion, the initial diameter of the brachial artery is larger in MESA participants diagnosed with sleep apnoea compared with undiagnosed people. However, the difference in flow-mediated dilation between these two cohorts is trivial when the flow-mediated response is scaled properly for resting diameter.

Keywords: Sleep apnoea; Endothelial function; Biostatistics; Allometry

Introduction

Analyses of the large dataset from the Multi-Ethnic Study of Atherosclerosis (MESA) indicate that physician-diagnosed sleep apnoea is associated with an increased risk of cardiovascular events [1]. The causal pathway between sleep apnoea and cardiovascular disease has been proposed to involve the intermediary variables of elevated sympathetic activity, insulin resistance and obesity [2]. Other abnormalities in coagulation factors, platelet activation, inflammatory processes and/or endothelial function could also play a role in the pathogenesis of cardiovascular disease in sleep apnoea [2].

Ali *et al.* [3] recently reviewed the utility of various early indicators of cardiovascular events in obstructive sleep apnoea. One of these indicators was the percentage flow-mediated dilation of the brachial artery (FMD%), which is an indicator of endothelial function in humans [4]. Ali *et al.* [3] reported that, in most studies, mean FMD% is lower for patients with obstructive sleep apnoea vs healthy participants; an observation corroborated by Hoyos *et al.* [5] in a recent review specifically on sleep apnoea and endothelial dysfunction.

From the earliest studies onwards, FMD% has been reported to be negatively correlated, sometimes strongly, to initial artery diameter [4, 6]. Despite some attempts to explain this observation physiologically, there is evidence to suggest that it is due to the poor size-scaling of the FMD% ratio index itself [7]. This confounding of FMD% is important because initial artery diameter has been reported to predict the progression of subclinical atherosclerosis [8] and cardiovascular events [9], as well as being substantially higher in obstructive sleep apnoea patients [10]. This obfuscation of arterial structure and function by the FMD% index is seldom resolved in the literature. For example, less than half of the thirteen studies on FMD% reviewed by Ali *et al.* [3] actually presented data for initial diameter. In only one of these studies [10] was there an attempt to adjust FMD% for initial diameter. Consequently, it has been questioned to what extent the reported lower FMD% in

obstructive sleep apnoea is explained by the potentially higher initial artery diameter in these patients [11].

Therefore, we aimed to quantify any differences in initial brachial artery diameter and flow-mediated dilation (adjusted for artery diameter) between people who did and did not report physician-diagnosed sleep apnoea in the dataset from the Multi-Ethnic Study of Atherosclerosis (MESA). This dataset has also recently been analysed to explore other questions related to sleep apnoea, predominantly because the dataset is very large, population-based and involved comprehensive and standardised data collection methods [1, 12-14].

Methods

The MESA participants

The full study design for MESA has been detailed by Bild *et al.* [15]. In brief, MESA is a prospective cohort study on subclinical cardiovascular disease. The overall MESA sample comprises 6814 women and men, aged 45–84 years, recruited from six regions in the USA. The MESA was approved by the local Institutional Review Boards of each participatory study site.

The sleep apnoea question in MESA

During the second MESA examination, a self-administered sleep history questionnaire was administered [1, 12-14]. A question was “*Have you ever been told by a doctor that you had sleep apnoea (a condition in which breathing stops briefly during sleep)?*” Participants responses were either “yes”, “no” or “*don’t know*”. Among the 6814 MESA participants, 678 either did not participate in the sleep history study or reported “*don’t know*” to the sleep apnoea question and were therefore excluded from analysis.

The FMD% protocol in MESA

Full details the FMD% protocol in MESA are described by Yeboah *et al.* [9]. Of the 6136 participants who recorded a yes/no answer for the sleep apnoea question, 3354 completed the FMD% protocol (1692 women and 1662 men). Of these participants, 104 (23 women and 81 men) reported that a physician had diagnosed them with sleep apnoea, giving an overall prevalence of 3.1% (1.4% in women and 4.9% in men).

Data analysis

Data were analysed using FMD%, and an allometric approach [6,16,17]. In this approach, initial and peak diameters are logarithmically transformed (natural logarithm) and the differences between these values are calculated. These differences in diameter on the log scale are entered as the outcome in a general linear model with sleep apnoea diagnosis as the fixed factor and logarithmically-transformed initial diameter as a covariate. The resulting adjusted estimates of the flow-mediated response and associated 95% confidence intervals (CI) are obtained after back-transformation. The allometric scaling exponent of 'b' is derived from the log-linear transformation of the simple allometric model based on the equation;

$$\text{Peak diameter} = a \times \text{initial diameter}^b$$

The FMD% and allometric approaches were compared using unadjusted models and models adjusted for sex, race and age. It is extremely important not to covariate-adjust statistical models for variables that are on the causal pathway between exposure and outcome [18]. This issue has been highlighted by Levitzsky and Redline [19] specifically in the context of obstructive sleep apnoea and cardiovascular disease. These authors thought it crucial not to adjust for variables such as body mass, diabetes and hypertension when the association between obstructive sleep apnoea and cardiovascular outcomes is being investigated because these variables are on the proposed causal pathway [2]. Therefore, these variables were not entered as covariates in our statistical models.

Any ratio index like FMD% is naturally positively skewed even if the numerator and denominator are normally distributed [17]. Therefore, the FMD% index was also examined following natural logarithmic transformation. Descriptive sample statistics are mean \pm standard deviation. The precision of inferential estimates is described by the 95% confidence limits.

Results

The correlation between FMD% and initial diameter was -0.43 (-0.57 to -0.26, $P<0.0005$) in the sleep apnoea patients (Figure 1) and -0.42 (-0.45 to -0.39, $P<0.0005$) in the undiagnosed participants. When FMD% was log-transformed, these correlations reduced slightly to -0.36 (-0.52 to -0.18, $P<0.0005$) and -0.40 (-0.43 to -0.37, $P=0.0005$) respectively. The regression slope for the FMD%-initial diameter relationship was -1.2 %/mm (95%CI: -0.7 to -1.7, $P<0.0005$) for sleep apnoea patients and -1.5 %/mm (95%CI: -1.4 to -1.6, $P<0.0005$) for undiagnosed participants.

The value of 'b' in the allometric model was 0.946 (0.924 to 0.969, $P<0.0005$) in the sleep apnoea patients and 0.942 (0.937 to 0.946, $P<0.0005$) in the undiagnosed cohort. Only when 'b' = 1.000 is a percentage index accurate for scaling a change in size across the full measurement range [16].

In the unadjusted model, the sample mean \pm SD estimate of FMD% was 3.8 \pm 2.6% for sleep apnoea patients vs 4.4 \pm 2.9% for undiagnosed participants (95%CI for difference: 0.01 to 1.14%, $P=0.045$, Table 1). In the model adjusted for sex, ethnicity and age, mean \pm SD estimates of FMD% remained unchanged (3.8 \pm 2.7 vs 4.4 \pm 2.7%) and the estimate of the difference between samples became more precise (95%CI: 0.07 to 1.12%, $P=0.028$).

In the unadjusted model, mean initial diameter was 0.45 mm larger in the sleep apnoea patients (95%CI: 0.28 to 0.61 mm, $P<0.0005$). This mean difference was 0.19 mm (95%CI: 0.07 to 0.32, $P=0.003$) in the model adjusted for sex, age and race. Use of the allometric approach to account for the confounding of initial diameter generally reduced the mean difference in flow-mediated response between sleep apnoea patients and healthy people. In the model adjusted only for initial artery diameter, the sample difference in adjusted flow-mediated dilation was 0.02% (-0.49 to 0.50, $P=0.92$). In the adjusted model, the difference between samples was 0.3% (95%CI: -0.1 to 0.7, $P=0.19$), which is approximately half the mean difference quantified with the FMD% index.

Discussion

It is vital that a ratio index scales consistently over the full range of measurements. In agreement with previous studies [6,16,17], the moderate-to-strong negative correlation between FMD% and initial diameter indicates that this assumption is also violated for sleep apnoea patients in the MESA (Figure 1). Our analyses suggest that the inappropriate scaling associated with FMD% leads to an exaggeration of the difference in flow-mediated response between people diagnosed with sleep apnoea and undiagnosed people in the MESA. Nevertheless, in agreement with previous studies [10], we found a clear mean difference in brachial artery diameter between people with and without sleep apnoea in the MESA.

Most of the past researchers on this topic have administered overnight sleep studies to their participants. Consequently, previous studies have tended to be relatively small and homogeneous in terms of participant sample [2]. A meta-analysis of the pooled mean difference in FMD% between people with and without sleep apnoea has yet to be undertaken on these past studies. However, Ali et al. [3] reported that this mean difference in FMD% tends to be 0.3-3.0%. The sample difference in FMD% in the present study of 0.6% lies within this range. A pertinent point is that statistical analyses have been covariate-adjusted for initial diameter in only one of these previous studies [10]. This research group

reported a substantial influence of initial artery diameter on the FMD% index. When the researchers adjusted for this confounding, the influence of a one-unit change in the Apnoea-Hypopnoea Index on FMD% was reported to be -0.09 % [10]. Therefore, the difference in FMD% (adjusted for initial diameter) between an apnoea-hypopnoea index of zero and twenty events/h can be estimated from this regression slope to be only 1.8%, which agrees with the clinically unimportant association found in our large population-based study.

The strengths of the present study were that it was large, population-based, multi-ethnic and involved comprehensive and standardized collection of data. Nevertheless, there are some limitations. First, our study was based on an observational cross-sectional design, which precludes the elucidation of the temporal relationships between variables in the causal pathway. Although it is thought most likely that sleep apnoea leads to endothelial dysfunction [2], the reverse could also be true. Interventions designed to improve the symptoms of sleep apnoea such as continuous positive airway pressure (CPAP) have been reported to improve FMD% in some studies [5], but none of these previous researchers has, again, covariate-adjusted the CPAP-mediated change in the flow-mediated response for any CPAP-mediated change in initial arterial diameter.

A second limitation is that the diagnosis of sleep apnoea was based on self-reported information, which may be influenced by recall bias. In MESA, it was questioned at the 2nd examination whether participants had ever been physician-diagnosed with sleep apnoea. The word “obstructive” was not included in the question. However, the prevalence of the other apnoeas (central and “mixed”) is known to be much lower than that of obstructive sleep apnoea [20]. Therefore, it is likely that the vast majority of the sleep apnoea patients in MESA had obstructive sleep apnoea. It is also likely that polysomnography was used to diagnose sleep apnoea in the MESA participants who reported diagnosis, since this method has been a part of the sleep apnoea clinical pathway for several decades in North America [21].

In conclusion, the sex, race and age-adjusted mean FMD% of the MESA participants who reported physician-diagnosed sleep apnoea was 0.6% lower than those who participants who did not report such a diagnosis. This mean difference was 0.3% and not statistically significant when the confounding influence of initial artery diameter was allometrically-adjusted for. Therefore, the MESA participants who reported physician-diagnosed sleep apnoea do not demonstrate a clinically important reduction in flow-mediated dilation.

Acknowledgement

This Manuscript was prepared using the Multi-Ethnic Study of Atherosclerosis (MESA) research materials obtained from the NHLBI Biologic Specimen and Data Repository Information Coordinating Center and does not necessarily reflect the opinions or views of the MESA or the NHLBI. MESA was supported by contracts N01-HC-95159 through N01-HC-95169 from the National Heart, Lung, and Blood Institute and by grants UL1-RR-024156 and UL1-RR-025005 from NCRR. The authors thank the other investigators, the staff, and the participants of the MESA (<http://www.mesa-nhlbi.org>).

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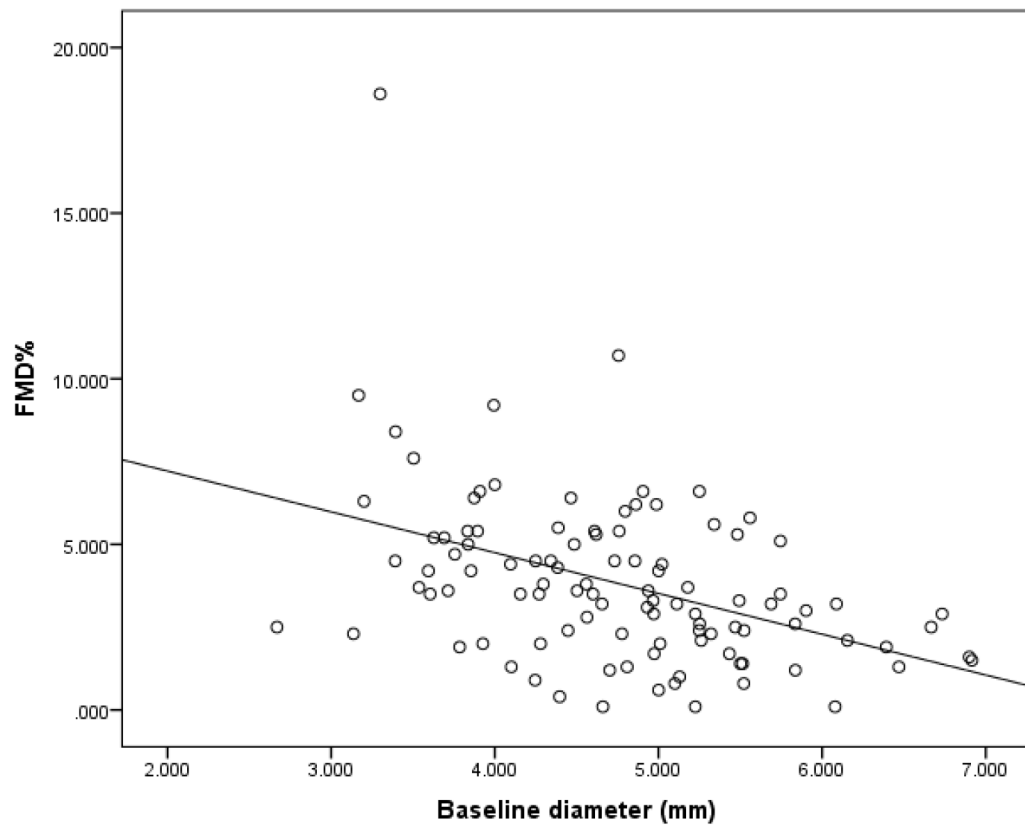
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Table 1. Variables measured during the flow-mediated dilation protocol for people in MESA who did, and did not, have physician-diagnosed sleep apnoea (Estimates not adjusted for race, sex and age).

Variable	Sleep apnoea (n=104) Mean \pm SD	Undiagnosed (n=3250) Mean \pmSD	95%CI for difference between samples
Initial diameter (mm)	4.76 \pm 0.89	4.31 \pm 0.83	0.28 to 0.61
Peak diameter (mm)	4.93 \pm 0.88	4.49 \pm 0.82	0.28 to 0.60
Absolute diameter change (mm)	0.17 \pm 0.10	0.18 \pm 0.11	-0.01 to 0.01
FMD% (%)	3.8 \pm 2.6	4.4 \pm 2.9	0.01 to 1.14
D_{base}-adjusted FMD (%)	4.4 \pm 2.4	4.3 \pm 2.4	-0.5 to 0.5

Figure 1. The negative moderate correlation between initial artery diameter and FMD% for the sleep apnoea patients in MESA.



Appendix Eight: Ethical approval for STOP-Bang work

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PRIVATE AND CONFIDENTIAL

Direct Line: 01642 384124

13th May 2014

Greg Atkinson
School of Health & Social Care
Teesside University

Dear Greg

Study No R071/14 - Does an exercise-related question improve the STOP-Bang's diagnostic utility?
Researcher: Sophie Suri. Supervisor: Greg Atkinson.

Thank you for submitting an application for Ethical Clearance via a Research Ethics Release Form.

I have **reviewed** and **approved** your application on 12th May 2014 and your study may proceed as it was described in your application pack.

Please note:

Where applicable, your study may only proceed when you have also received written approval from any other ethical committee (e.g. NRES) and operational / management structures relevant (e.g. Local NHS R&D). If applicable please forward to me a copy of the approval letter from NRES before proceeding with the study.

In all cases, should you wish to make any substantial amendment to the protocol detailed, or supporting documentation included, in your approved application pack (other than those required as urgent safety measures) you must obtain written approval for those, from myself and all other relevant bodies, prior to implementing any amendment. Details of any changes made as urgent safety measures must be provided in writing to myself and all other relevant bodies as soon as possible after the relevant event; the study should not continue until written approval for those changes has been obtained from myself and all other relevant bodies.

On behalf of the School of Health & Social Care Research Governance and Ethics Committee please accept my best wishes for success in completing your study.

Yours sincerely

A handwritten signature in black ink, appearing to read 'Alasdair MacSween'.

Dr. Alasdair MacSween

Chair
Research Governance and Ethics Committee
School of Health & Social Care

VAT REG NO. GB 686 4809 81



INVESTOR IN PEOPLE

Appendix Nine: R and D approval for STOP-Bang



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15th May 2014

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Phd Student
Teesside University
Parkside West
Middlesbrough
TS1 3BA

Dear Sophie

Re: SUR1 – 150514 - Does an exercise-related question improve the STOP-Bang's diagnostic utility?

Thank you for submitting your application form to Research and Development.

Following review, it has been concluded that your work falls into the category of Service Evaluation and poses no unacceptable governance or ethical issues.

Therefore, R&D has approved your Service Evaluation and wishes you well with your study.

Kind regards.

A handwritten signature in black ink, appearing to read "A Owens".

Mr A Owens
Research & Development Director
GMC 3485934

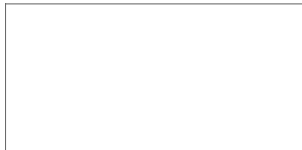
Appendix 10: BSWMS referral form

Referral form for Bariatrics and Specialist Weight Management Services

Service: Bariatric ☐ SWMS ☐

South Tees ☐
North Tees/Hartlepool ☐

Patient details
(please place patient sticker here)



Referring person:

Height (m): Collar size (cm):

Weight (Kg): Age (yrs):

BMI (kg/m²):

STOPBANG

S - Snore
T - Epworth ≥ 12
O - Apnoea
P - BP

YES

NO

B - BMI >35
A - Age > 50
N - Neck $> 40\text{cm}$
G - Gender: Male

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Final Score (/ 8)
Epworth (/ 24)

Relevant co-morbidities:

Cardiac: MI/Angina ☐ Cardiac failure ☐ Arrhythmia ☐
Respiratory: COPD ☐ Asthma ☐ Smoker ☐
Diabetes: ☐ Renal ☐

Other:

Physical Activity

Do you routinely participate in any physical activity or exercise (either on your own or with others) to improve or maintain your physical fitness? YES ☐ NO ☐

When walking during everyday activities, do you find that you have to walk slower than other people? YES ☐ NO ☐

Oximetry

Quality control: Pass ☐ Fail ☐

ODI (dips per hour):

Likely diagnosis OSA: YES ☐ NO ☐

Mean saturation:

Likely severity: Mild ☐ Moderate ☐ Severe ☐

RDI:

Plan: Sleep Clinic Review ☐ Discharge ☐

Sleep Clinic Review

CPAP YES ☐ NO ☐

Discharge YES ☐ NO ☐

Screening Sleep Consultant:
(Name/position/reg no.)

Sleep OP Assessment:
(Name/position/reg no.)

Appendix 11: Research passport for JCUH

South Tees Hospitals 

NHS Foundation Trust

Research & Development / Academic Division
Academic Centre
The James Cook University Hospital
Marton Road
Middlesbrough
TS4 3BW

www.southtees.nhs.uk

Tel: 01642 282585

Email: julie.rowbotham@stees.nhs.uk

24th June 2014

Sophie Suri
PhD Student
School of Health and Social Care
Teesside University
Parkside West
Middlesbrough
TS1 3BA

Dear Sophie,

Letter of Access for Research – Projects Specific

Does an exercise-related question improve the STOP-Bang's diagnostic utility?

Designing and conducting an exercise intervention and analysis of data generated from pre and post outcome measures

This letter confirms your right of access to conduct research through South Tees Hospitals NHS Foundation Trust for the purpose and on the terms and conditions set out below. This right of access commences on 24th June 2014 and ends on 23rd June 2017 unless terminated earlier in accordance with the clauses below.

You have a right of access to conduct such research as confirmed in writing in the letter of permission for research from this NHS organisation. Please note that you cannot start the research until the Principal Investigator for the research project has received a letter from us giving permission to conduct the project.

The information supplied about your role in research at South Tees Hospitals NHS Foundation Trust has been reviewed and you do not require an honorary research contract with this NHS organisation. We are satisfied that such pre-engagement checks as we consider necessary have been carried out.

You are considered to be a legal visitor to South Tees Hospitals NHS Foundation Trust premises. You are not entitled to any form of payment or access to other benefits provided by this NHS organisation to employees and this letter does not give rise to any other relationship between you and this NHS organisation, in particular that of an employee.

While undertaking research through South Tees Hospitals NHS Foundation Trust, you will remain accountable to your employer **University of Teesside** but you are required to follow the reasonable instructions of **Professor Danjoux** in this NHS organisation or those given on her/his behalf in relation to the terms of this right of access.

Where any third party claim is made, whether or not legal proceedings are issued, arising out of or in connection with your right of access, you are required to co-operate fully with any investigation by this NHS organisation in connection with any such claim and to give all such assistance as may reasonably be required regarding the conduct of any legal proceedings.

You must act in accordance with South Tees Hospitals NHS Foundation Trust policies and procedures, which are available to you upon request, and the Research Governance Framework.

You are required to co-operate with South Tees Hospitals NHS Foundation Trust in discharging its duties under the Health and Safety at Work etc Act 1974 and other health and safety legislation and to take reasonable care for the health and safety of yourself and others while on South Tees Hospitals NHS Foundation Trust premises. You must observe the same standards of care and propriety in dealing with patients, staff, visitors, equipment and premises as is expected of any other contract holder and you must act appropriately, responsibly and professionally at all times.

You are required to ensure that all information regarding patients or staff remains secure and *strictly confidential* at all times. You must ensure that you understand and comply with the requirements of the NHS Confidentiality Code of Practice (<http://www.dh.gov.uk/assetRoot/04/06/92/54/04069254.pdf>) and the Data Protection Act 1998. Furthermore you should be aware that under the Act, unauthorised disclosure of information is an offence and such disclosures may lead to prosecution.

You should ensure that, where you are issued with an identity or security card, a bleep number, email or library account, keys or protective clothing, these are returned upon termination of this arrangement. Please also ensure that while on the premises you wear your ID badge at all times, or are able to prove your identity if challenged. Please note that this NHS organisation accepts no responsibility for damage to or loss of personal property.

We may terminate your right to attend at any time either by giving seven days' written notice to you or immediately without any notice if you are in breach of any of the terms or conditions described in this letter or if you commit any act that we reasonably consider to amount to serious misconduct or to be disruptive and/or prejudicial to the interests and/or business of this NHS organisation or if you are convicted of any criminal offence. Your substantive employer is responsible for your conduct during this research project and may in the circumstances described above instigate disciplinary action against you.

South Tees Hospitals NHS Foundation Trust will not indemnify you against any liability incurred as a result of any breach of confidentiality or breach of the Data Protection Act 1998. Any breach of the Data Protection Act 1998 may result in legal action against you and/or your substantive employer.

If your current role or involvement in research changes, or any of the information provided in your Research Passport changes, you must inform your employer through their normal procedures. You must also inform your nominated manager in this NHS organisation.

Yours sincerely

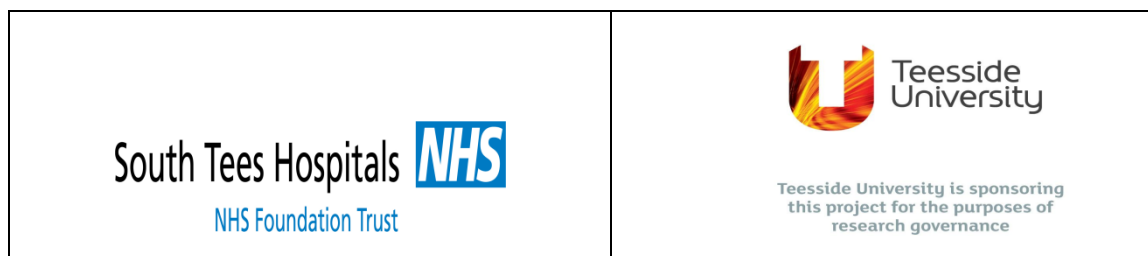


Julie Rowbotham
R&D Manager,
South Tees Hospitals NHS Foundation Trust

Cc: Professor Danjoux
Consultant Anaesthetist
Cheriton House
The James Cook University Hospital

Sally Dent
Human Resources
University of Teesside

Appendix 12: Public involvement questionnaire



Individualized exercise training before and after bariatric surgery in patients with obstructive sleep apnoea: A feasibility study

Patient Sex: Male/Female

Patient referral pathway: Specialist Weight Management / Bariatric

Teesside University and South Tees Hospitals NHS Foundation Trust (STHNHSFT) are working together to develop a research study to explore the possibility of taking some exercise prior to and after weight management surgery when a person has also been diagnosed with sleep apnoea.

We are seeking your views, which will be invaluable in helping us to design a future research project. Opinions of patients are very important in ensuring research studies are of high quality. Therefore, we would be very grateful if you could take a few minutes to complete the following questions regarding aspects of a potential study. There are no right, or wrong, answers. Rather we are seeking your opinion about the best way to conduct this research.

Our future study will involve people who have been given a date for weight management surgery and have also been diagnosed with “sleep apnoea”, whereby breathing is very difficult during sleep. We want to help this group of people to do some exercise before and after their surgery because we believe this will help them cope with the surgery, reduce the days spent in hospital after surgery and improve sleep apnoea symptoms. We would appreciate your views on how easy or difficult you think it would be to participate in such a study.

Your help

The following questions will be asked by Sophie Suri, who is undertaking a postgraduate degree at Teesside University on this topic of sleep apnoea and exercise.

1. How important do you think increasing your levels of exercise and fitness might be for improving your current health status?

- ☐ Very important
- ☐ Important
- ☐ Somewhat important
- ☐ Not important at all

2. How would you feel about doing some supervised exercise lasting for a maximum of 1 hour, twice a week, at Teesside University if your travel expenses were paid for?

- ☐ Fine
- ☐ A little Concerned
- ☐ Very Concerned
- ☐ I wouldn't do it

3. How would you feel if this exercise was done in short “chunks” lasting 30-60 seconds where you would become out of breath but then there would be some rest periods in between?

- ☐ Fine

☐ A little Concerned

☐ Very Concerned

☐ I wouldn't do it

4. Would you be willing to keep a written log of how much physical activity/exercise you do during every-day activities?

☐ Yes

☐ No

5. Would you be willing to wear a pedometer type tracker (worn on the waist) to measure how much physical activity/exercise you do during every-day activities?

☐ Yes

☐ No

6. Anyone who is involved in this study would have about a 33% chance of being allocated to a no-exercise "control" group rather than the group who receive the exercise training. Here, you would receive all the treatment you would normally get, but you would not be given any supervised exercise. However, health measurements would be obtained from you at various times before and after your surgery. Would this affect your willingness to be involved in the study?

☐ Yes

☐ No

7. Which health measures *(you can choose more than 1)* would you want to improve in the study?

- ☐ Symptoms of sleep apnoea
- ☐ Length of hospital stay after surgery
- ☐ Exercise capacity (fitness)
- ☐ Your weight
- ☐ Health related quality of life (including; feelings of tiredness, feelings of being in control and feelings of anxiety and/or depression)
- ☐ Physical activity (how active you are)

8. During a study, feedback from patients about the exercise programme is very important. How would you feel most comfortable providing us with this information if you were in this position?

- ☐ Interview (a one on one informal discussion with the researcher)
- ☐ Telephone Interview (the researcher will phone you at a convenient time)
- ☐ Focus group (a group discussion with other patients and the researcher)
- ☐ Survey (a written survey completed at your postoperative clinic appointment)

9. Hypothetically, would you be interested in participating in a study of this kind?

☐ Yes

☐ No

If NO, could you explain reasons why you would not want to participate?

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Do you have any suggestions regarding questions we could ask in the interview/focus group/surveys to determine your thoughts about the exercise completed during the study?

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If you have any further suggestions or comments about issues we have not covered please feel free to write these below

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On behalf of the team at Teesside University and at STHNHSFT, thank you for taking the time to complete this form. Your opinions are very valuable in improving the quality of the research conducted at JCUH.

Kind regards

Prof. Greg Atkinson

Professor of Health Sciences Research
Teesside University

Prof. Gerard Danjoux

Consultant (Sleep Medicine and Anaesthesia)
South Tees Hospitals NHS Foundation Trust